

Review article

Haemodialysis-associated anaphylactic and anaphylactoid reactions

Anaphylactic and anaphylactoid reactions related to haemodialysis have been increasingly described for almost 3 decades. The majority of these cases used to occur with ethylene oxide sterilized, and complement-activating cellulose membranes. However, a considerable number of publications have focused on polyacrylonitrile AN69[®] high flux membranes, angiotensin converting enzyme inhibitors and iron as other important causes of potentially severe haemodialysis-related anaphylactoid reactions. Clinical manifestations vary considerably and generally do not allow differentiation between IgE-mediated anaphylaxis and anaphylactoid reactions (e.g. from nonspecific mediator release). Successful management of these patients requires multidisciplinary approach and involves prompt recognition and treatment by the attending physician, and identification of the offending agent(s) with subsequent avoidance of the incriminated compound(s). This review focuses on some major causes of anaphylactoid and anaphylactic reactions during haemodialysis. Special consideration is given to the therapeutic and diagnostic approach.

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Key words: allergy; antiseptics; bradykinin; erythropoietin; ethylene oxide; formaldehyde; haemodialysis; heparin; iron; latex; polyacrylonitrile (AN69[®]).

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Accepted for publication 9 August 2005

Reporting of acute anaphylactoid reactions during haemodialysis starts in 1975 (1). A considerable number of papers describing severe and potentially life-threatening immediate hypersensitivity reactions have been published, but well-conducted prospective epidemiological surveys remain rare.

Data collected by the Food and Drug Administration showed that in 1982 there were 3.5 severe hypersensitivity reactions per 100 000 hollow-fibre dialysers sold, with an estimate of five deaths per year within the entire US dialysis population (2, 3).

In a study by Daugirdas et al. (4), 21 severe reactions to haemodialysis, including four cardiac arrests and one fatality, occurred in approximately 260 000 dialysis treatments. In an analysis performed by Simon et al. (5), in 1536 patients (including in 30 dialysis units and 122 694 haemodialysis sessions) the prevalence of anaphylactoid reactions was calculated. Thirty-three anaphylactoid reactions in 21 patients (1.3%), of which eight severe anaphylactoid reactions in five patients (0.25%) were observed with an annual incidence of 0.17 per 1000 sessions with cellulose membranes and 4.2 per 1000 sessions with synthetic membranes.

Successful management of haemodialysis-associated anaphylaxis and anaphylactoid reactions requires a multidisciplinary approach. Correct management requires prompt recognition and immediate stopping dialysis, without returning the blood to the patient. The next step includes adequate symptom-based treatment, and correct identification of the offending agent(s) with subsequent avoidance of incriminated compounds.

This review focuses on some major causes of anaphylactoid and anaphylactic reactions during haemodialysis. Special consideration is given to the therapeutic and diagnostic approach.

Clinical manifestations

Dialysis-associated anaphylactoid and anaphylactoid reactions generally present as an acute event. The symptoms may be mild to moderate with pruritus, erythema, flushing, fainting, rhinoconjunctivitis, urticaria and angio-edema. However, in a considerable number of reports more severe to life-threatening reactions with bronchospasm, larynx oedema, bradycardia, hypoten-

sion, shock, cardiac and/or respiratory arrest and death have been described. Generally, symptoms are rapid-onset; beginning almost immediately (within minutes) after the blood is being returned from the dialyser or filtration device to the patient. Signs can also be delayed and appear from 15 to 45 min after the start of haemodialysis [as is the case with reactions to local antiseptics and natural rubber latex (NRL)]. They result from absorption through skin, mucosal surfaces and soft tissue of the allergen. On the contrary, symptoms may initially not be recognized as a manifestation of hypersensitivity.

In general, clinical manifestations do not allow to discriminate between IgE-mediated anaphylaxis and non-IgE-mediated anaphylactoid reactions, resulting from nonspecific release of mediators, such as histamine or LTC₄. Isolated angio-edema might point to bradykinin accumulation. Figure 1 summarizes the most relevant pathomechanisms involved in haemodialysis-associated anaphylactic and anaphylactoid reactions.

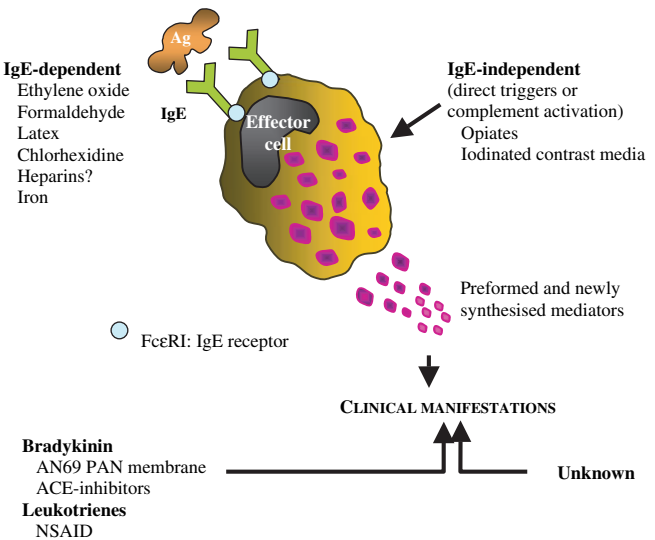


Figure 1. Mechanisms involved in haemodialysis-associated anaphylactic and anaphylactoid reactions. Effector cells (i.e. mast cells and basophils) can be activated through cross-linking of FcεRI-bound specific IgE (anaphylaxis). Preformed mediators (e.g. histamine, heparin) are released rapidly while arachidonic acid metabolites (e.g. leukotriene D₄ and prostaglandin D₂) and cytokines (e.g. IL-4) are synthesized released more slowly. Effector cells can also be triggered independently of IgE (anaphylactoid reaction). Either directly or via the anaphylatoxins C3a and c5a. Furthermore, ‘hypersensitivity’ manifestations might also result from a nonimmune mediated mechanism. For example, through accumulation of the potent vasodilator bradykinin (excessive production through contact phase activation by the AN69 polyacrylonitrile (PAN) membrane or decreased degradation of bradykinin by inhibition of angiotensin converting enzyme (ACE) by ACE-inhibitors), or accumulation of leukotrienes by inhibition of cyclooxygenase isotype 1 by nonsteroidal inflammatory drugs (NSAID).

Aetiology

Table 1 summarizes the most important agents involved in immediate anaphylactic and anaphylactoid hypersensitivity reactions during haemodialysis.

Ethylene oxide

Ethylene oxide (EtO) is a potent alkylating compound of high chemical reactivity, and has been widely used for gas sterilization of biomedical devices, that do not tolerate heat sterilization. It is extremely irritating in high concentrations and even in low concentrations it is capable to alter native protein and potentially creating neo-antigens (6, 7). Poothullil et al. (1), in 1975, first reported on a patient suffering from anaphylaxis to EtO immediately after the onset of the haemodialysis session. The original hapten hypothesis that EtO, conjugated to protein (mostly human serum albumin), could act as an allergen was proposed by Dolovich and Bell (8), as many others have described systemic IgE-mediated allergy to EtO-protein conjugates in medical settings, particularly during haemodialysis (9–24). Moreover, as the majority of these reactions occurred during the first use of dialysers (and not when dialysers were re-used), EtO has been identified as the main cause of the ‘first use syndrome’ (25). In contrast, the presumption that hypersensitivity reactions from EtO were related to activation of complement (26) could not be confirmed (27).

Diagnosis of EtO-mediated anaphylaxis is generally based upon history and serology, i.e. quantification of a

Table 1. Mechanisms and diagnostic procedures organised on the basis of most important causes of haemodialysis-associated anaphylactic/anaphylactoid reactions*

	Latex	EtO	Heparin	ACEI/AN69®	Antiseptics
Pathomechanism	IgE	IgE	Unknown	Bradykinin	Unknown
History	S	S	S	S	S
slgE	S	S	NA	NR	NA
SPT	S	NA	S ¹	NR	S ¹
IDT	NR	NA	S ¹	NR	S ¹
SCT	NR	NR	S ¹	NR	NR
BAT	S	NA	S	NR	S
LTT	NR	NA	S	NR	S
ScPT	NR	NR	S ²	NR	NR

Although for heparins and antiseptics it is put the pathomechanism is generally unknown, there is some evidence for IgE-mediated anaphylaxis (see text). ACEI, angiotensin converting enzyme inhibitor; AN69®, polyacrylonitrile; slgE, specific IgE; SPT, skin prick test; IDT, intradermal test; SCT, subcutaneous test; BAT, basophil activation test; ScPT, subcutaneous provocation test; S, standard procedure; NA, not available; NR, not relevant; A, available.
S¹ – serial dilution with suspected drug starting with SPT. Subsequently IDT and SCT only when former test remains negative and if appropriate. In the event of life-threatening reactions, only an alternative noncross-reactive drug is tested *in vivo*. S² – with alternative drug that was tested negative in SPT, IDT, LTT and BAT.
*As performed at the department of Immunology, Allergology and Rheumatology of the University Hospital Antwerp.

commercially available EtO-specific IgE, basophil activation tests and skin tests (8, 15, 19, 21, 22, 28–30).

Improved degassing techniques, thoroughly rinsing new dialysers and tubing, and replacing EtO by steam or gamma radiation to sterilize dialysers, may help (but not always, e.g. EtO originating from the dialyser potting) circumvent this problem (31–33).

Formaldehyde

Formaldehyde (HCOH) is a low molecular weight organic chemical with numerous industrial applications in the manufacturing of plastic, rubber, resins, coatings, resins and adhesives. Formaldehyde is also used as a disinfecting, preserving and embalming agent. For a comprehensive description of the major health hazards including IgE-mediated and delayed type hypersensitivity (DTH) reactions of formaldehyde the reader is referred elsewhere (21, 34–39). Apart from occupational exposure, sources for anaphylaxis from formaldehyde are haemodialysis (21, 40–42) and dental/orthodontic treatment (43–49). Actually, evidence for an IgE-mediated reaction towards formaldehyde was first provided in a patient on haemodialysis by Maurice et al. in 1986 (50).

Polyacrylonitrile membranes

In 1990 Tielemans et al. (51) reported on five life-threatening anaphylactoid reactions, occurring within the first minutes of haemodialysis on high-flux polyacrylonitrile AN69[®] capillary dialysers in three patients receiving ACE inhibitors. As numerous publications have focused on these generally severe (and sometimes fatal) anaphylactoid reactions in patients dialysed or haemofiltrated on these electronegative charged AN69[®] membranes, both with (5, 51–58) and without concomitant ACE-inhibitor intake (5, 52, 54, 57) or, albeit to a lesser extent, angiotensin receptor antagonist therapy (59, 60). In some of these patients, anaphylactoid reactions stopped when the AN69[®] membrane was replaced by another membrane (cellulosic or synthetic) (5, 53, 56). With regard to the mechanism(s) of these 'hypersensitivity' reactions, evidence has emerged that contact phase activation by the negatively charged polyacrylonitrile membrane can increase bradykinin concentrations (51, 61–63). Bradykinin increases inducible nitric oxide synthase activity, leading to higher production of nitric oxide (NO). NO is a short-lived gas, which exerts its potent vasodilating activity (which may lead to angio-edema and shock) via increased cGMP in smooth-muscle vascular cells (57, 64). By impairing kinin degradation, ACE-inhibitors can further increase bradykinin concentrations to pathological levels, allowing the full development of the clinical picture (65). At present, there are no readily available assays to quantify bradykinin, and diagnosis relies upon history and/or revision of the medical notes and/or exclusion of other causes. Whether the use of an

alkaline rinsing solution is a valuable alternative for change of dialysis membrane remains to be elucidated (66). Other conditions, which result in accumulation of bradykinin such as congenital and acquired forms of C1 esterase inhibitor deficiency also may preclude application of acrylonitrile membranes (67, 68).

Meanwhile, a surface-treated AN69 ST[®] membrane is available which does not lead bradykinin release and these anaphylactoid reactions (69).

Natural rubber latex

During the past 2 decades IgE-mediated allergy to the constituent proteins of NRL has become an important and well-recognized condition with defined risk groups. Current findings indicate that NRL allergy is more prevalent in (powdered) NRL glove-wearing workers, particularly healthcare workers, and in individuals with a history of multiple surgical interventions, such as children with spina bifida, meningomyelocele, bladder exstrophy and anorectal anomalies. Some of these patients may develop end stage renal failure and need haemodialysis (70). Whether patients with chronic renal failure represent an independent risk group for IgE-mediated NRL allergy remains to be established. According to skin prick tests (SPT), Kalpaklioglu et al. found sensitization to NRL in 3/286 (1.1%) nonatopic patients on chronic haemodialysis (71). Diagnosis of IgE-mediated NRL allergy generally involves quantification of latex-specific IgE and latex skin testing (72), but additional *in vitro* tests such as the basophil activation test (73) and appropriate provocations can also be helpful (see below). Currently, avoidance with the use of alternative elastomers such as polyvinylchloride, neoprene, nitrile, tactylon and polyurethane remains the only correct management of patients with NRL allergy.

Heparins

Heparins are used for thromboprophylaxis in patients undergoing haemodialysis, haemofiltration or continuous renal replacement therapies. In many of these indications the unfractionated heparins (UFH), are sometimes being replaced by low molecular weight heparins (LMWH) because of the improved pharmacokinetic and pharmacodynamic properties, as well as a better safety profile of the latter (74, 75).

A major immune-mediated adverse reaction is heparin-induced thrombocytopenia (HIT) type II, without and with (fatal) thrombosis (76–84). It is a complex clinical syndrome with significant morbidity and mortality, if unrecognized. The platelet count typically falls below generation of pro-coagulant platelet-derived microparticles. Other pro-coagulant effects of the HIT antibody include endothelial cell damage, stimulation of platelet-leucocyte aggregates, and release of tissue factor from monocytes [for review: (85)].

As a minimum of 12–14 saccharides seems to be required to form the antigenic complex with PF4, HIT type II is generally observed with the use of UFH and rarely with LMWH. Specific recommendations for optimal management of HIT are given elsewhere (86, 87).

Immediate hypersensitivity reactions to heparins comprise rhinoconjunctivitis, asthma, urticaria, angio-edema and generalized potentially life-threatening anaphylaxis [recently summarized in (88)]. It is not known whether pre-existing DTH to heparins predisposes to other immune-mediated adverse reactions, such as immediate hypersensitivity or HIT type II, but one should always be alert to this possibility.

Subcutaneous challenge with heparins is accepted as the most reliable method to identify DTH reactions to heparins, whereas patch tests (even with delayed readings after 96 h) yield a high rate of false-negative results (89–92). Subcutaneous provocation is also recommended to determine safe treatment options for patients allergic for specific heparins.

For safety reasons, for identification of the offending drug, as well as an appropriate safe alternative anticoagulant regimen, *in vitro* tests such as lymphocyte transformation and basophil activation and/or appropriate skin tests should precede subcutaneous challenge tests (88, 89, 93–96). Heparinoids, such as danaparoid, that mainly consists of heparan sulphate cannot be recommended as a substitute for UFH or LMWH, but should be included in the testing programme of patients (90, 91, 93).

Finally, it is emphasized that ‘heparin allergy’ might also result from sensitization to excipients, including preservatives such as paraoxybenzoic esters (parabens) (97).

Iron

Iron deficiency is the major cause of poor response to recombinant human erythropoietin (rhuEPO) in patients suffering from end-stage renal failure, undergoing haemodialysis. Because supplementation with oral nonheme iron is generally disappointing, a considerable number of patients on haemodialysis require intravenous iron therapy to maintain adequate haemoglobin concentrations and/or to lower the rhuEPO dose (98). Currently, available intravenous iron preparations include iron dextran, iron gluconate and iron sucrose. These compounds clearly differ with respect to their molecular weight, pharmacokinetic and dynamic characteristics, and drug-related adverse events. Particularly the administration of iron dextran, even a minute test dose (99, 100), can result in potentially life-threatening allergic reactions (100–105). Review of drug reporting databases by Faich and Strobos (104) identified 31 fatalities attributed to the use of intravenous iron dextran. In addition, it appears that there is no method currently available to predict which patients will suffer from such

reactions, as these might occur despite a <<negative>> test dose and after several uncomplicated exposures. While pseudoallergic reactions usually occur during the first exposure to iron dextran, anaphylactic reactions can occur after multiple uneventful administrations (105). Iron dextran is composed of iron oxide crystals, surrounded by a matrix of cross-linked dextrans. These dextrans are well known to elicit IgE and IgG antibody-mediated reactions. On the contrary, iron gluconate and sucrose formulations, containing iron oxide polymers rather than crystals, and no immunogenic dextrans, have been consistently reported to be well-tolerated and rarely to induce (severe) allergic reactions, even in patients with life-threatening allergic reactions to iron dextran (105–109).

Miscellaneous

Anaphylactoid reactions towards rhuEPO remain anecdotal and might result from sensitisation to an excipient, such as gelatine and polysorbate (110, 111) rather than the active compound itself (112). Antiseptics constitute another potential source of haemodialysis-associated hypersensitivity. Chlorhexidine, an antiseptic belonging to family of biguanides, is used extensively in the medical and surgical environment. Delayed-type hypersensitivity reactions occur regularly and are well-documented events. Conversely, immediate hypersensitivity, presenting as acute urticaria that can result in anaphylactic shock, is rarer [for recent review: (113)]. These sometimes life-threatening manifestations can even occur from simple skin application (114). Recently, life-threatening anaphylaxis to povidone–iodine (betadine®), another commonly applied topical antiseptic solution, has been reported (115–117).

Acute management

Treatment of haemodialysis-associated anaphylactoid or anaphylactic reactions depends on the type of reaction and its severity. Stop of dialysis session, without returning the blood to the patient and cessation of eventual drug supply is the first measure, followed by adequate general and specific individualized procedures, according to the general rules of emergency treatment (118–121).

Epinephrine should be administered to all patients with clinical signs of hypotension, shock, airway angio-oedema, or definite breathing difficulty. The maximum initial dose of epinephrine is 0.2–0.5 mg in adults and 0.01 mg/kg to a maximum of 0.3 mg in children, routes of injection subcutaneous *vs* intramuscular. In the absence of clear clinical improvement administration of epinephrine can be repeated after 5 min. The doses of epinephrine recommended for children are summarized in Table 2. Epinephrine should not be administered intravenously except for profound shock that is immediate life-threatening. If given,

Table 2. Doses of intramuscular epinephrine in children and adults

Age (years)	Volume of 1 : 1000	Dose (µg)
<2	62.5 (1 : 1000 dilution)	62.5
2–5	0.125	125
6–11	0.25	250
>11	0.5	500
Adults	0.5	500

For a posology of epinephrine in mg/kg, the reader is frequently referred to the paper by Simons (121). However, it should be acknowledged that in this paper a serious dosage error appears in the section 'Epinephrine in the first aid treatment of anaphylaxis' (p. 837). *The maximal initial dose is 0.2 to 0.5 mg in adults and 0.01 mg/kg to a maximum of 0.3 mg in children.* (See erratum, *J All Clin Immunol* 2004;113:1039).

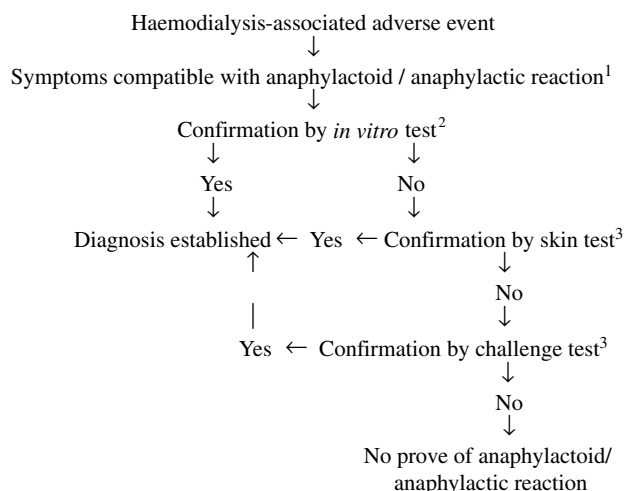
a dilute solution 1 : 10 000 (never 1 : 1000) should be injected as slowly as seems reasonable with cardiac monitoring. Antihistamines should be used in the management of all anaphylactic and anaphylactoid reactions, and are generally administered intramuscularly. Obviously, antihistamines should never be administered alone to treat severe systemic anaphylaxis with respiratory and cardiovascular symptoms. Corticosteroids, generally given intravenously may avert late phase reactions and should be administered in any case of an anaphylactic or anaphylactoid reaction. An inhaled β_2 -agonist is useful as an adjunctive measure if bronchospasm is a major feature of the reaction. Key additional interventions for refractory or deteriorating situations are addressed elsewhere. Airway, breathing, circulation and level of consciousness should be assessed carefully.

Diagnosis

Identification of the offending material(s) and potential cross-reactive compound(s) is an absolute prerequisite for effective management, i.e. appropriate secondary prevention. Careful history taking of the patient (and, if necessary the treating physician) and thorough revision of the medical record are mandatory for correct diagnosis, but objective tests are needed for confirmation. Diagnostic methods for identification of the offending compound(s) comprise, depending on the mechanism, skin tests, serology (quantification of specific IgE), lymphocyte transformation and basophil activation assays, and, eventually *in vivo* challenge tests. These investigations should be postponed until 4–6 weeks after the anaphylactic episode, because of IgE and/or basophil or mast cell mediator depletion or possible influence on these test by medication used to treat the events (e.g. corticosteroids). Figure 2 represents a diagnostic algorithm.

History

In obtaining the history, several points should be considered; (a) extent of symptomatology, (b) time



¹Quantification of tryptase during the acute event can be helpful to discriminate with other types of reaction.

²*In vitro* tests have rarely been validated. Prudence is called upon their interpretation.

³Skin and challenge tests have to be performed according to existing guidelines.

Figure 2. Diagnostic algorithm.

elapsed between start of haemodialysis session and onset-of symptoms, (c) materials used (e.g. membrane, tubing, connection, sterilization procedure, dialysate, antiseptics), (d) previous (drug) allergies or intolerances and concomitant drug administration, (e) underlying conditions [atopy, congenital pathology (spina bifida, myelodystrophy), C1-esterase inhibitor deficiency].

Quantification of serum tryptase

Quantification of total serum tryptase can provide important information with regard to the underlying mechanism of haemodialysis-associated 'hypersensitivity' reactions. Mast cells and basophils that have been activated during an anaphylactic or anaphylactoid reaction, release tryptase that can be quantified in the patients' serum. An increase in total tryptase can be measured in serum 30 min after the first allergic manifestations. Tryptase's half-life is 2 h, and the levels gradually decrease over time, or it may remain elevated for days in cases of late-onset, biphasic, and protracted reactions. However, elevated levels of total tryptase in patients with chronic renal failure have been reported (122), and may indicate an increased mast cell burden, because of high levels of stem cell factor. Consequently, in such patients, mature tryptase might be a more specific marker of effector cell degranulation (123).

Absence of increased serum tryptase does not rule out an anaphylactic or anaphylactoid reaction. Serum histamine is not quantified routinely because of its half-life of only a few minutes.

Specific IgE

Except for NRL, EtO, formaldehyde and chlorhexidine, immunoassays to quantify serum specific IgE antibodies are not readily available.

Skin tests

Drugs account for the majority of dialysis-associated anaphylactic and anaphylactoid reactions. Generally, diagnostic work-up of such reactions starts with skin tests that should not be carried out earlier than 4–6 weeks after the acute event (see above).

Skin prick tests are performed on the anterior part of the forearm, using a drop of diluted and subsequently undiluted drug. Skin prick tests are considered positive when the wheal and flare reaction equal or exceed 3 mm. A positive (e.g. histamine) and negative (e.g. buffer solution) control have always to be performed at the same time.

For intradermal testing (IDT) injection of 0.05 ml of commercially available drugs diluted in a 0.04% phenol physiological solution is performed through a hypodermic needle and reactions are read after 15–30 min, by measuring diameters of wheals and flares. It is advisable to restrict IDT to patients with negative SPT results. Results are considered positive when the wheal exceeds 5 mm. General considerations for skin test procedures in drug hypersensitivity are summarized in Ref. (124). As cutaneous responses may be decreased in patients with chronic renal failure (125), one should always take care to include an appropriate positive (i.e. histamine) and negative (i.e. buffer solution) control.

In the context of dialysis-associated immediate hypersensitivity, skin tests have proven to be helpful in the diagnosis of allergy towards EtO, NRL, heparins, formaldehyde and chlorhexidine.

Lymphocyte transformation test

The lymphocyte transformation test (LTT) measures the proliferation of T cells to an antigen or mitogen *in vitro*. Although LTT is classically considered as a reflection of cellular immunity, positive LTT can be obtained in typically IgE-mediated situations, probably due to the stimulation and expansion of T-helper cells (126, 127). For a recent overview about the technical aspects, applicability, interpretation and limitations of the LTT in drug allergy the reader is referred elsewhere (128). According to dialysis-associated immediate hypersensitivity reactions, the LTT has proven to be positive to different compounds such as heparins and chlorhexidine. For diagnosis of IgE-mediated NRL allergy, the LTT is too insensitive, as compared with quantification of latex-specific IgE and the NRL skin test (129).

Basophil activation assays

Basophils activated with specific allergen that cross-bridges surface receptor FcεRI-bound IgE, not only secrete and generate bioactive markers such as histamine and LTC₄, but also up-regulate the expression of activation antigens, such as CD63 and CD203c.

Basophil histamine release assays have been described in the literature since 1960 (130). However, the utility as a tool to diagnose drug allergy remains rather disappointing, with an overall sensitivity of 50% and specificity of 35–60%, respectively (131, 132).

The role of sulphidoleukotriene release in the diagnosis of drug allergy is limited to nonsteroidal anti-inflammatory drugs (NSAID) and β-lactam antibiotics. For NSAID the sensitivity has been reported to vary between 20% and 70%, whereas the specificity generally exceeded 80%, for β-lactam antibiotics, sensitivity and specificity of the assays varied between 35–80% and 80–90%, respectively [reviewed in Refs (133, 134)].

For diagnosis of IgE-mediated NRL allergy, both mediator release tests perform poorly (135).

The discovery of the basophil activation antigens, such as CD63 and CD203c, has induced the development of a flow cytometric technique to analyse allergen-specific *in vitro* activation of basophils. The principles and aspects of flow-assisted allergy diagnosis are reviewed in Ref. (136). The technique has been applied for the diagnosis of allergy to pollen, house dust mite, food, NRL, hymenoptera venoms, as well as drugs such as muscle relaxants (137), β-lactam antibiotics (138), metamizol (139) and NSAID (140). In our hands flow cytometric analysis of activated basophil was proven to offer a confirmatory test in a number of drug hypersensitivities for which no other *in vitro* test is available (88, 141, 142). In some of these patients, the basophil activation test proved useful to tailor the therapeutic alternative.

Challenge tests

Considering the risk for potentially life-threatening hypersensitivity reactions, challenge tests with suspected drugs are not recommended, and, except for subcutaneous challenges with heparins (see above) and local anaesthetics, such provocations have never been recommended on a systematic base. However, in clinical practice it might be necessary to perform appropriate challenge tests with (unrelated) compounds as an ultimate ratio measure to identify a safe alternative. Description of the different provocation protocols is beyond the scope of this review but is addressed in (143). Most importantly, *in vitro* tests and skin tests with the intended alternative(s), should precede all types of provocation, whenever possible. Because of risk involved for the patient, such investigations should only be performed in specialized centres.

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