

Research: Care Delivery

A practical, clinical approach to the assessment and management of suspected insulin allergy

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Abstract

Background Although allergic reactions to insulin are uncommon, they can be difficult to diagnose and management may be very difficult in subjects with Type 1 diabetes with severe allergy. Access to allergists and specialist diagnostic tests is limited and few diabetes specialists are familiar with desensitization as a means of treating allergy. People with diabetes may develop symptoms which mimic insulin allergy but are attributable to other conditions.

Case reports Here we describe three cases of insulin allergy. One patient presented with severe, albeit localized, urticarial reactions at injection sites. The most severe case was a woman with recent-onset Type 1 diabetes who presented with grade 2 anaphylaxis. The third patient presented with generalized urticaria and angioedema. Insulin allergy was confirmed in all three cases.

Methods Assessment involved measurement of immunoglobulin and anti-insulin antibody levels. Skin testing was performed in two cases. Treatments included desensitization in one case, alternative insulin preparations, antihistamines and continuous subcutaneous insulin infusion. In all three cases of insulin allergy there has been successful resolution of symptoms.

Conclusions The clinical assessment and investigation in cases of suspected insulin allergy is described, along with detailed algorithms for skin testing and desensitization. This case series demonstrates an approach to challenging cases of suspected insulin allergy which will be helpful for diabetes specialists.

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Introduction

Insulin therapy for Type 1 diabetes (and increasingly for Type 2 diabetes) has been based on insulin injections for more than 80 years. While immune reactions to bovine and porcine insulins were common in the past, it was thought that allergic reactions would decrease with the introduction of recombinant human insulins [1]. While the prevalence of allergic reactions did appear to decrease with recombinant human insulin, cases of allergic reactions to human insulin were reported and insulin analogues proposed as an alternative strategy to circumvent these allergic reactions [2,3]. However, with the widespread adoption of analogues, more recent reports have described allergic reactions to both rapid-acting and long-acting insulin analogues [4–6].

Recent estimates of the prevalence of insulin allergy suggest that it complicates diabetes management in 0.1 to 3% of patients treated with insulin [7]. Although reactions may be attributable to allergies to various components of

insulin preparations, including impurities and additives such as zinc, protamine and metacresol, in many cases it is the recombinant human insulin itself acting as the allergen [8]. Others have speculated that microbial components of the yeast or bacteria used to synthesize recombinant human insulin or insulin analogues may be the allergen. Alteration of epitopes or protein mis-folding during the manufacture and purification of insulin may also be responsible. This may be important with the emergence of bio-similar insulin preparations.

The most commonly described allergic reaction to human insulin is an immunoglobulin E (IgE)-mediated type I immediate hypersensitivity reaction [7], usually localized at the injection site. In some cases a more generalized reaction can occur, with angioedema or anaphylaxis. As with many peptides administered therapeutically by subcutaneous injection, antibodies (anti-insulin IgG antibodies) are commonly found in the circulation of people treated with insulin, but are not usually associated with clinical symptoms [9,10]. However, other conditions may be confused with insulin allergy and a sound approach to diagnosis and management is essential.

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While the assessment and management of mild cases of insulin allergy may be straightforward, if the first principles for managing any allergic reaction are applied, the management of more severe cases can be very challenging [5]. Firstly, in Type 1 diabetes, it is not possible to avoid the allergen. Secondly, specialist advice may be difficult to access and immunological investigations may take some time before results become available, thus management decisions must often be made prior to diagnosis. Furthermore, there is little literature to provide practical advice for the clinical management of these difficult cases in the acute stages, before investigations permit a definitive diagnosis.

Thus, although insulin allergy is relatively rare, it can be a very challenging clinical problem. Here we describe the investigation and management of three cases of suspected insulin allergy encountered between 2006 and 2009. We also provide a detailed description of a method for skin testing and a protocol for desensitization that could be utilized if access to specialist immunological advice is not readily available.

Case 1 (also see Table 1)

A lean 65-year-old man (BMI 20.2 kg/m²) with a 1.5-year history of diabetes mellitus secondary to total pancreatectomy (for pancreatic cancer) presented with severe localized skin reactions at his injection sites that appeared almost immediately after insulin injection. These reactions were characterized by induration, erythema and pruritis and were only minimally relieved by the use of an over-the-counter oral antihistamine. At presentation he was taking NPH insulin (Humulin N; Eli Lilly, Toronto, ON, Canada) twice daily and insulin lispro (Humalog; Eli Lilly) with each meal. A trial of insulin preparations from another manufacturer (Novolin NPH and insulin aspart; Novo Nordisk, Mississauga, ON, Canada) did not lead to any improvement in his symptoms. His past medical history was otherwise significant only for hypertension and his medications included aspirin, ramipril and pancreatic exocrine supplements (cotazyme, Schering). He had no prior history of allergies either to drugs or environmental allergens.

Investigations (see Table 1) revealed good glycaemic control (HbA_{1c} 56 mmol/mol, 7.3%) and high levels of anti-insulin antibodies (42% bound, normal < 3%), but normal total IgE levels (38 IU/ml, normal < 120). Test doses of several insulin preparations were administered in the clinical investigation unit by the diabetes specialist to document and confirm an allergic reaction to insulin with the hope that an insulin preparation with no reaction might be identified. The skin testing protocol is shown in Box 1. Briefly, 1:20 dilutions (11) of 10 insulin preparations (including recombinant human, analogue and porcine insulin preparations) were prepared with sterile normal saline by the hospital pharmacy. 50 µl of each solution was injected intradermally using a conventional insulin syringe (each dose of '5 units' delivered 0.25 units

of insulin). Normal saline was used as a negative control. Reactions were graded by measuring the diameter of wheal and redness at each injection site and recorded on a skin testing worksheet (see also Supporting Information, Appendix S1).

Box 1 Intradermal Insulin Skin Testing Protocol*

Setting

- Testing should be conducted in a setting with access to resuscitation facilities.
- Equipment to treat anaphylaxis should be on hand, as per local policy, e.g. oxygen, epinephrine (1:1000 aqueous solution), diphenhydramine (50mg), intravenous fluid

Preparation

- Have pharmacy prepare insulin products to be tested as 1:20 dilutions in sterile normal saline [30].
- Subjects should take their usual basal insulin dose on the evening prior to testing and attend fasting.
- Antihistamines should be discontinued prior to testing.

Monitoring

- Capillary blood glucose and vital signs should be monitored each hour.
- Hypoglycaemia can be treated with oral or intravenous glucose as per local policies.

Testing

- 50 µl of each preparation is injected intradermally on anterior forearm with a standard U-100 insulin syringe (i.e. 5 'units' on syringe = 0.25 units of insulin)
- 50 µl of sterile normal saline is injected as a negative control.
- 50 µl of 0.001 mg/ml histamine may be injected as a positive control.
- Test injections are spaced at least 3 cm apart.
- Skin tests are read after 15 min. If a delayed reaction is suspected the skin tests are read at 6 and 24 h.
- Observations can be recorded on the insulin allergy skin testing worksheet (see Supporting Information, S1).

* For allergies in general, skin prick testing should precede intradermal testing in case of a severe reaction [25]. Intradermal testing can be used to confirm life-threatening insulin allergy (summary statement 122, in [26]).

The skin test results are illustrated in Fig. 1. Skin reactions appeared rapidly and remained positive at 15 min (when it is recommended that skin tests are read, as early reactions that do not persist may simply reflect an irritant response) for all insulin preparations tested. The greatest reactions (based on the size of wheal) were to the recombinant human insulin preparations (30–33 mm). The least severe reactions were against detemir (14 mm), followed by glargine (18 mm), porcine NPH (18 mm) and aspart (22 mm).

Subsequently, the patient's diabetes was treated using detemir twice daily and lispro with meals. In addition, he was prescribed the antihistamine, cetirizine, 10 mg daily. His skin reactions gradually resolved over several months and his symptoms remain controlled more than 4 years later, albeit with regular dosing with cetirizine.

Case 2

An overweight 40-year-old woman was diagnosed with diabetes mellitus having presented to the emergency depart-

Table 1 Clinical characteristics, interventions and outcomes of four subjects with suspected insulin allergy

Case	Age (years)	Gender	Type of diabetes	Duration of diabetes	Other allergies	Insulin therapy	Insulin dose ($\text{U kg}^{-1} \text{ day}^{-1}$)	Presenting features	Investigations	Skin testing	Intervention	Outcome
1	65	Male	Surgical diabetes (secondary to total pancreatectomy)	1.5 years	Nil	Humulin N and lispro	0.5	Localized urticaria	Total IgE 38 IU/ml (normal < 120); anti-insulin antibodies 42% bound (normal < 3%*)	Positive	Humulin N switched to detemir; antihistamine	Resolution of symptoms
2	40	Female	Type 1	4 months	Animal dander, pollen, family history of atopy	Detemir and aspart	0.4	Dyspnoea, wheeze, angioedema	Total IgE 423 IU/ml (normal < 120); anti-GAD 3.59 (< 0.02); anti-insulin 13.9	Not done	Desensitization performed to aspart; continuous subcutaneous insulin infusion; antihistamine	Resolution of symptoms
3	49	Female	Type 2	19 years	Sulpha drugs, family history of seasonal allergies	Novolin NPH and Novolin Toronto	0.5	Urticaria, angioedema, tachypnea, tachycardia	Total IgE 282 IU/ml (normal < 120); anti-insulin antibodies (IgG) 13.6 IU/ml (normal < 0.4 IU/ml†)	Positive	Glucocorticoids and antihistamines given acutely Insulin discontinued; oral anti-hyperglycaemic agents started	Resolution of symptoms

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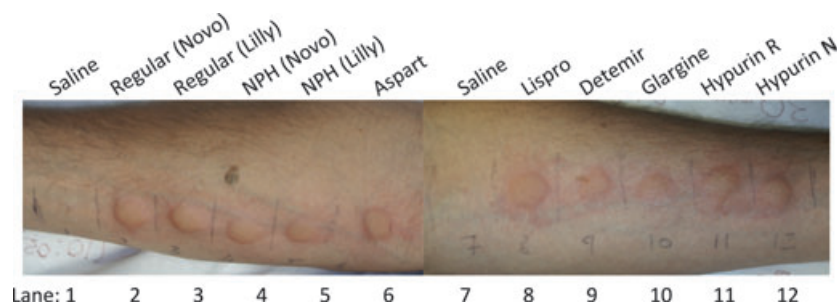


FIGURE 1 Photos of skin reactions 30 min after test doses of insulin preparations given intradermally to the subject described in case 1. Wheals surrounded by erythema can be seen in response to all insulins tested, which persist beyond 30 min, and indeed 240 min (not shown). Immunoglobulin E (IgE)-mediated allergic reactions are confirmed by the presence of wheal and flare after 15–20 min as reactions that appear earlier, but do not persist, may simply be attributable to an irritant response. As a control, 50 μ l of normal saline was injected in lanes 1 and 7. In lanes 2–6 and 8–12, 50 μ l of various insulin preparations diluted 1 in 20 with normal saline (to a final concentration of 5 units/ml, which is the concentration of insulin used in the Novo Insulin Allergy Kit [11], but which is no longer available) were injected. The insulin preparations tested were: lane 2, regular (Novolin Toronto; Novo Nordisk); lane 3, regular (Humulin R; Lilly); lane 4, NPH (Novolin NPH; Novo Nordisk); lane 5, NPH (Humulin N; Lilly); lane 6, aspart (Novorapid; Novo Nordisk); lane 8, lispro (Humalog; Lilly); lane 9, detemir (Levemir; Novo Nordisk); lane 10, glargine (Lantus; Sanofi-Aventis); lane 11, porcine regular (Hypurin Neutral; CP Pharmaceuticals); lane 12, porcine NPH (Hypurin Isophane; CP Pharmaceuticals).

ment with diabetic ketoacidosis and being treated with fluids and intravenous insulin. A day or two after switching to subcutaneous insulin using glargine and lispro she developed generalized urticaria, wheezing and perioral paresthesias. These symptoms settled with treatment with antihistamines (diphenhydramine) and inhaled β -agonists and switching the insulin preparations used to detemir and aspart. A few weeks after discharge from hospital she was able to discontinue the antihistamine and β -agonist therapy.

Four months later she had an anaphylactic reaction characterized by generalized urticaria, angioedema, dyspnea and wheeze, which was treated in the emergency department (with epinephrine, methyl prednisolone, diphenhydramine and salbutamol), and subsequently discharged. This episode appeared to have been provoked by the use of lispro (instead of her usual aspart) for breakfast and lunch, having forgotten her own insulin. The following day, despite taking her usual dose of aspart with breakfast, she presented to the emergency department again with a similar episode of anaphylaxis. She was transferred to a local intensive care unit for further management.

The patient's past history was significant for allergies to grass pollen and animal dander. There was a strong family history of allergies and atopy. On examination her BMI was 40.7 kg/m² and vitals were stable. By the time of transfer, there was mild lip swelling but no wheeze, hives or localized reactions near her injection sites. Laboratory investigations (see Table 1) revealed modest glycaemic control (HbA_{1c} 65 mmol/mol, 8.1%). Total IgE levels, measured 2 weeks later, were elevated (423 IU/ml, normal < 120) and autoantibodies (anti-GAD and anti-insulin) were positive. Thyrop-eroxidase antibodies were also positive (827 kU/l; normal < 50 kU/l), although thyroid-stimulating hormone (TSH) was normal (0.66 mU/l) and anti-nuclear antibodies were

negative. Insulin autoantibodies were also measured independently by Dr G. Eisenbarth (University of Colorado, Denver, CO, USA) and confirmed to be positive (1.496 nmol/l; normal < 0.01 nmol/l). Fasting C-peptide and glucose levels were 0.61 nmol/l (normal 0.30–1.32 nmol/l) and 17.3 mmol/l, respectively.

In the intensive care unit, the patient was treated with intravenous hydrocortisone (25 mg every 6 h) and intravenous diphenhydramine (50 mg every 8 h). No respiratory or ventilatory support was required. Initially, an intravenous infusion of regular insulin (Novolin Toronto diluted in sterile normal saline) was started at 0.01 units/h. The patient reported a peri-oral tingling sensation and the infusion held, while the patient fasted overnight. Blood glucose and ketones were monitored throughout. A low carbohydrate diet (40 g/day) was used to minimize her insulin requirements. She did not become ketotic.

Desensitization was performed the following day in the intensive care unit with insulin aspart using the protocol shown in Box 2 (adapted from Grammer [12]), although no basal insulin was used in this case. On the low carbohydrate diet the blood glucose was stable at *c.* 17 mmol/l, but steadily decreased when she was receiving 1 unit of aspart subcutaneously/h (level 10 on the desensitization protocol). Because continuous subcutaneous insulin infusion was not available acutely, and aspart's duration is insufficient to maintain suppression of hepatic glucose production overnight, a basal insulin was required. She was therefore given a small test dose of detemir with no reaction. Detemir (4 units) was started at bedtime and the dose slowly titrated up each day. She was discharged 3 days later on aspart 4 units with meals, detemir at bedtime, an oral antihistamine (initially diphenhydramine and cetirizine) and an epinephrine autoinjector for emergency use.

Box 2 Insulin Desensitization Protocol (adapted from Grammer [12])**Setting**

- Testing should be conducted in a setting with access to resuscitation facilities.
- Equipment to treat anaphylaxis should be on hand, as per local policy, e.g. oxygen, epinephrine (1:1000 aqueous solution), diphenhydramine (50 mg), intravenous fluid.

Preparation

- Have pharmacy prepare three serial dilutions of the insulin product to be used for desensitization
 - Prepare solution A (1 in 10) as a 1:10 dilution of U-100 insulin by adding 1 ml of insulin to 9 ml of sterile normal saline.
 - Prepare solution B (1 in 100) by adding 1 ml of solution A to 9 ml of sterile normal saline.
 - Prepare solution C (1 in 1000) by adding 1 ml of solution B to 9 ml of sterile normal saline.
- Subjects should take their usual basal insulin* dose on the evening prior to testing and attend fasting. (*In an inpatient or intensive care unit setting, intravenous insulin has been suggested to be safe to maintain euglycaemia and prevent ketoacidosis [33]).
- Intravenous access should be established.

Monitoring

- Capillary blood glucose and vital signs should be monitored each hour.
- Hypoglycaemia can be treated with oral or intravenous glucose as per local policies.

Desensitization

- The initial injection is of 10 µl of solution C (1 in 1000); this corresponds to 1 'unit' on a standard U-100 insulin syringe (in this case only 0.001 units of insulin will actually be delivered).
- Injections of solution C are given intradermally. Injections of solution A and B are given subcutaneously.
- The injection site is marked.
- After 20–30 min, any local or systemic reaction is recorded on the worksheet.
- If no reaction has been observed, move to the next level for the next injection (see table).
- If a reaction is noted, either stay at the same or move back a level for the next injection.
- The process is repeated until undiluted U-100 insulin can be injected without any reaction.

Table Schedule of injections for desensitization in insulin allergy (adapted from Grammer [12])

Level	Route	Solution	Dilution	True insulin dose (units)	Volume to be injected (µl)	Number of 'units' on U-100 insulin syringe
1	Intradermal	C	1:1000	0.001	10	1
2	Intradermal	C	1:1000	0.002	20	2
3	Intradermal	C	1:1000	0.005	50	5
4	Subcutaneous	B	1:100	0.01	10	1
5	Subcutaneous	B	1:100	0.02	20	2
6	Subcutaneous	B	1:100	0.05	50	5
7	Subcutaneous	A	1:10	0.1	10	1
8	Subcutaneous	A	1:10	0.2	20	2
9	Subcutaneous	A	1:10	0.5	50	5
10	Subcutaneous	Insulin	Undiluted	1.0	10	1

Over the next 4 months she continued to have mild symptoms (lip and tongue paresthesias) after each insulin injection. She was switched to continuous subcutaneous insulin infusion with aspart. Now, 3 years later she has had no further anaphylactic reactions while on continuous subcutaneous insulin infusion and takes an oral antihistamine occasionally for mild episodes of urticaria.

Case 3

A 49-year-old woman with a 19-year history of Type 2 diabetes (Table 1) was assessed on an urgent basis after developing an anaphylactic reaction to insulin. For many years she had been maintained on oral agents, but, because of suboptimal control, basal insulin (NPH; Novolin NPH; Novo Nordisk) had been added at bedtime 6 months prior and was tolerated well. However, her oral agents were discontinued with the addition of regular insulin (Novolin Toronto; Novo Nordisk) at meals as part of a multiple daily

injection regimen and 3 weeks later she developed generalized urticaria several hours after a dose of regular insulin. Despite over-the-counter antihistamines her symptoms progressed. Thirty-six hours later she presented to the emergency department with urticaria, angioedema and dyspnea such that she was unable to complete sentences. She was tachycardic and tachypneic but not hypotensive. She improved after treatment with intravenous glucocorticoids and antihistamine.

The patient's past medical history was significant for hypothyroidism, hypertension, obesity (BMI 38.7 kg/m²), a ruptured appendix and two Caesarean sections. Her medications included levothyroxine, diltiazem and aspirin, and she had an allergy to sulphonamide (sulpha) drugs. Her family history included her father had Type 2 diabetes, her brother had Type 1 diabetes and her sister and uncles had coeliac disease. Laboratory investigations (Table 1) revealed modest glycaemic control (HbA_{1C} 67 mmol/mol, 8.3%), elevated IgE levels and positive anti-insulin antibodies.

Although thyroid peroxidase (TPO) antibodies were positive (123 kU/l; normal < 50 kU/l), thyroid-stimulating hormone was normal (0.67 mU/l on replacement) and anti-transglutaminase antibodies were negative. Fasting plasma glucose, insulin and C-peptide levels (17.6 mmol/l, 49.4 mU/l; normal 5.0–20.0 mU/l, 2.22 nmol/l; normal 0.30–1.32 nmol/l, respectively) were consistent with Type 2 diabetes.

Intradermal skin testing by an allergist demonstrated reactions to detemir, glargine, Humulin R, Humulin N and lispro. She did not react to Novolin NPH or to aspart.

As there was evidence of endogenous insulin production, insulin was discontinued and oral hypoglycaemic agents resumed in combination with intensified lifestyle management. There has been significant weight loss and improvement in glycaemic control with no further allergic reactions.

Discussion

An allergy to insulin was confirmed in all three cases described here. Diabetes management was challenging during the period before investigations to permit definitive diagnosis to be completed.

Reactions to animal insulins (beef and pork) have been reported since the 1920s [13]; however, reactions to human recombinant insulin are far less common, with reports of prevalence ranging from 0.1 to 3% [7]. Many clinicians are aware of the potential for additives and preservatives such as metacresol, zinc and protamine to act as allergens [5], but few seem aware that insulin itself contained in pharmaceutical preparations is usually the allergen. This is probably because clinically significant allergic reactions to insulin are uncommon and the immunology not well understood.

The most common type of allergic reaction to human insulin is the type I immediate hypersensitivity reaction. This is an IgE-mediated reaction, with the release of vasoactive substances such as histamine from basophils and mast cells. The presentation can range from a localized wheal-and-flare reaction at the injection site to generalized urticaria and angioedema [8]. Anaphylactic reactions have been described previously [6,14] and in rare cases can be fatal [15]. All three of our subjects with confirmed insulin allergy had type I hypersensitivity reactions. Circulating IgE levels were elevated in the two subjects who presented with systemic symptoms (subject 2 and subject 3), but were normal in subject 1. Thus, while elevated IgE levels are supportive, their absence does not exclude a diagnosis of insulin allergy. It is possible to specifically measure anti-insulin IgE antibodies and their absence would make a type 1 hypersensitivity reaction to insulin unlikely. Care should be taken, however, as, in the presence of very high levels of total IgE, elevated specific IgE may represent a false positive.

Anti-insulin antibodies are found almost universally in people treated with insulin [16], so it is not surprising that they were found in all of our subjects, as all had been treated with exogenous insulin, for months or years. It is very

uncommon for these antibodies to have clinical sequelae, although very rarely anti-insulin antibodies may cause insulin resistance (because of inactivating insulin antibodies) [17,18] or hypoglycaemia (as in the insulin autoimmune syndrome where anti-insulin antibodies in the circulation act as a reservoir for insulin) [19]. These and other immune reactions to insulin have been recognized for many years [20] and seem to be attributable to IgG antibodies. Although the anaphylactic reactions to insulin in our cases appear to be attributable to IgE antibodies, there are animal data indicating that anti-insulin IgG antibodies can cause fatal anaphylaxis [21].

An approach to assessment, investigation and management of suspected insulin allergy is presented in Table 2. The approach is presented in a linear format for simplicity and clarity, but we recognize that many aspects of assessment and treatment may need to be performed in parallel, with revisions as the clinical situation unfolds. Alternatively, it may be reasonable in cases with a mild localized reaction at injection sites to move straight to therapy, for example try a different brand of insulin, without more detailed investigation.

Diagnosis involves a thorough history and physical examination. Any suspicion of latex allergy should be followed by testing. Some insulin vials have bungs containing latex [22], which could contaminate the needle when insulin is being drawn up. Many needles use silicone or other lubricants that could act as allergens. Switching needles and/or moving to a latex-free delivery device, especially in subjects with suspected latex allergy, seem sensible first steps until test results are available.

It is important that other causes such as poor injection technique and other skin or allergic disorders should be excluded [23]. The importance of this has been underscored by our experience with a patient with Type 1 diabetes who developed idiopathic urticaria, where insulin allergy was excluded by both negative skin tests and negative anti-insulin IgE levels.

Skin testing is considered the gold standard to confirm insulin allergy [6] and either skin prick or intradermal testing may be performed [24]. For the diagnosis of allergies in general, skin prick testing is the initial test because of the potential for severe reactions [25]. Skin prick tests are read after 15–20 min and wheals > 3 mm in diameter are deemed to be positive [25].

The skin tests performed on the patient in case 1 used doses and concentrations of insulin used in the allergy test kits, which previously were supplied by Novo Nordisk [11]. Although skin prick testing would have been preferred by some allergists, the test doses were administered intradermally to our subject. American Practice Parameters indicate that intradermal testing can be used to confirm insulin allergy (summary statement 122 in [26]), which may be more sensitive than skin prick tests for some drugs including insulin (summary statement 25 in Bernstein *et al.* [25]).

Table 2 An approach to assessment and treatment of suspected insulin allergy

Assessment (in all cases)	Severity	Investigation	Management options
Type of reaction (local, systemic, cutaneous, anaphylactic)	Mild	Exclude reaction to needles confirm reaction to insulin	Change needles Change insulin preparation Antihistamine <i>pro re nata</i> (e.g. chlorpheniramine, diphenhydramine)
Temporal and spatial relationship with insulin administration	Moderate	Total IgE	Non-sedating antihistamine regularly: loratadine, desloratadine, fexofenadine, cetirizine
Changes or interruptions in insulin therapy		Insulin-specific IgE	Topical corticosteroid
Insulin preparations used	Severe or persistent	Anti-insulin antibodies	Inhaled β -agonist if bronchospasm
History of atopy or other allergies (latex)		Autoantibodies	
Consider alternative explanations—other medications (angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs)		Random glucose and C-peptide	
—any changes in diet, cosmetics, detergents?		Prick or intradermal skin testing (see Box 1)	H1 + H2 antihistamine (loratadine plus ranitidine) $\pm$ sedating antihistamine
—other autoimmune disease? [systemic lupus erythematosus (SLE), Graves]		Complement levels, C1-INH	If Type 2 diabetes, discontinue insulin
Review diabetes diagnosis—Type 1 vs. Type 2. Is it possible to discontinue insulin?		Exclude viral or bacterial causes for urticaria (hepatitis, cytomegalovirus, Epstein-Barr virus)	Intravenous insulin (short term)
		Consultations with dermatology/immunology/rheumatology	Insulin pump ($\pm$ addition of hydrocortisone)
			Desensitization (see Box 2)
			Leukotriene receptor antagonist
			Systemic steroids
			Omalizumab (anti-IgE monoclonal antibodies)
			Systemic immunosuppression
			Pancreas transplant

Measurement of serum insulin-specific IgE and IgG antibodies can be helpful, and total IgE may also be elevated [8]. It should be noted that free IgE levels may appear to be low if measured during the acute episode as a result of consumption.

In patients with Type 2 diabetes, discontinuation of insulin can be considered with a switch to oral hypoglycaemic agents and/or glucagon-like peptide 1 (GLP-1) agonists. It is not possible to avoid the antigen by discontinuing insulin in people with Type 1 diabetes or diabetes as a result of total pancreatectomy.

Initial management includes the use of antihistamines, and switching to a different insulin preparation. In more severe allergic reactions, more than one antihistamine drug may be combined and consideration may even be given to including an H-2 antagonist (e.g. fexofenadine 360 mg in the morning combined with cetirizine 20 mg and ranitidine 300 mg in the evening). Systemic steroid therapy may be required, but causes hyperglycaemia and insulin resistance, further increasing exposure to the allergen (because increased insulin doses are required). There have been reports of mixing small quantities of glucocorticoid with insulin to reduce local reactions associated with injections or continuous subcutaneous insulin infusion [27], which should avoid the adverse effects associated with systemic steroids.

Both corticosteroids and antihistamines are commonly used as adjunctive treatments in patients with anaphylaxis (as in case 2). However, there is no strong evidence for the effectiveness of corticosteroids to prevent biphasic anaphylaxis [28] or for antihistamines [29].

If none of these solutions is effective, desensitization [5,30] can be performed using a protocol similar to that described

in Box 2, adapted from Grammer [12]. We used a more rapid approach, similar to that described by Lee *et al.* [31], than that taken by Matheu *et al.* [2]. The rapid desensitization protocol of Lee *et al.*, developed in oncology for allergies to chemotherapeutic drugs, is robust and consistently effective and has been used in both in- and outpatient settings [31]. *In vitro* studies suggest that a step-wise dose increase over time results in a desensitization where both early and late mast cell activation responses, and internalization of the antigen/IgE/Fc ϵ RI complexes are inhibited, but which is antigen specific [32].

We also used intradermal injections for the initial doses, as per Grammer [12], who notes that many physicians prefer to use the subcutaneous route for desensitization exclusively. Desensitisation can be carried out using continuous subcutaneous insulin infusion [2] if desired and/or available, and may be performed with very low initial basal rates (i.e. 0.01 U/h), with small increments as tolerated [6]. To avoid the development of ketoacidosis during desensitization, concomitant intravenous insulin infusions have been used [2,33]. The mechanism for the apparent lack of immunogenicity with intravenous insulin remains uncertain, and caution must be exercised as our patient in case 2 described symptoms in response to intravenous insulin. The fact that she did not develop ketoacidosis during her desensitization was likely attributable to the presence of residual endogenous insulin production in recent-onset Type 1 diabetes.

Continuous subcutaneous insulin infusion has been described in several reports as effective maintenance therapy in patients with insulin allergy [7]. A consistent theme in case reports of insulin allergy seems to be that the risks of reactions are increased by intermittent exposure to insulin,

particularly if there are interruptions in therapy. This seems to be illustrated by case 2, where anaphylaxis seems to have been provoked by exposure to lispro after a 4-month interval. Continuous exposure to insulin, for example with continuous subcutaneous insulin infusion, seems to help maintain the 'tolerant' state. We are not in a position to determine whether we have achieved desensitization (absence of reaction with regular exposure to antigen) or true tolerance (no requirement for ongoing exposure to antigen to avoid reaction), but ongoing insulin therapy is required in cases 1 and 2.

A recent case report described the successful use of omalizumab, a monoclonal anti-IgE antibody, in a patient with insulin allergy recurring after previous desensitization [34]. Pancreas transplant has also been successful in curing severe, refractory insulin allergy [35,36]. Islet transplantation might also be considered. These approaches would only be considered if all other approaches had been unsuccessful.

In summary, insulin allergy is an uncommon complication of insulin therapy, but one which is encountered by many clinicians who treat patients with diabetes. We have described three patients with diabetes who developed insulin allergy, of whom two presented with dramatic, systemic symptoms. While initially it was clear unclear whether discontinuation of insulin might be an option in cases 2 and 3, all three patients were successfully treated either by switching to a different insulin, by desensitization and continuous subcutaneous insulin infusion, or by switching to oral hypoglycaemic agents in the patient with Type 2 diabetes. We present clinically relevant tools to assist with diagnosis and treatment of this challenging situation. These cases illustrate the clinical heterogeneity of this condition, the importance of establishing the correct diagnosis and the need for individualized therapy.

Footnote

The clinical approach and tools presented in this manuscript are not intended to replace specialist immunologic advice case or clinical practice guidelines. In particular we would refer the reader to guidelines published by the American Academy of Allergy, Asthma and Immunology and European Academy of Allergy and Clinical Immunology [25,26].

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Competing interests

JJ and CLC have nothing to declare. PAS has received honoraria and/or grant support from Novo Nordisk, Lilly, Sanofi, Medtronic and Animas.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Insulin allergy skin testing worksheet.

Appendix S2. Insulin desensitization worksheet.

Insulin Allergy Skin Testing Worksheet

Name:	Date				Start Time							
	Lane 1	Lane 2	Lane 3	Lane 4	Lane 5	Lane 6	Lane 7	Lane 8	Lane 9	Lane 10	Lane 11	Lane 12
Test Insulin												
Time (min)	Wheal / Flare	Whea/ Flare I	Wheal/ Flare	Wheal/ Flare	Wheal/ Flare	Wheal/ Flare	Wheal/ Flare	Wheal/ Flare	Wheal/ Flare	Wheal/ Flare	Wheal/ Flare	Wheal/ Flare
15-20*	/	/	/	/	/	/	/	/	/	/	/	/
	/	/	/	/	/	/	/	/	/	/	/	/
	/	/	/	/	/	/	/	/	/	/	/	/
	/	/	/	/	/	/	/	/	/	/	/	/
	/	/	/	/	/	/	/	/	/	/	/	/
comments												

Record diameter of wheal and flare (erythema) in mm (26). * for diagnosis of allergy, peak reactivity for skin prick tests is 15 to 20 minutes while Intracutaneous tests are read after 10 to 15 minutes (summary statements 9 & 24, in ref 25). Reactions observed prior to 15 minutes (which do not persist) may represent an irritant response. Clinicians may wish to assess resolution of any reactions by recording observations at later time points, which may be useful for guiding the choice of insulin preparation for ongoing therapy.

Insulin Desensitization Worksheet

Name:

Date[illegible]