

A CLINICAL APPROACH TO THE INVESTIGATION OF SUSPECTED VACCINE ANAPHYLAXIS

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ABSTRACT

Vaccine anaphylaxis is rare, despite the increased incidence of atopic disease and food allergies and an increase in the number of vaccines administered to young children. The mechanism of vaccine anaphylaxis is poorly understood and may be IgE- or non-IgE- mediated. The first step is to assess if the reported symptoms and signs are consistent with anaphylaxis, using the Brighton Collaboration case definition of anaphylaxis. Skin-prick and intradermal testing may support the diagnosis. If vaccine anaphylaxis is diagnosed, re-vaccination with the same vaccine antigens or other vaccines containing the same excipients is contraindicated, but the risk of anaphylaxis to other vaccines is not increased. The measles, mumps, rubella (MMR) and influenza vaccines are safe in egg-allergic children. Influenza vaccination in children with egg anaphylaxis may be given under specialist medical supervision. Misdiagnosis of vaccine anaphylaxis may prevent an individual from receiving vaccinations, possibly resulting in a vaccine-preventable illness. All healthcare providers must report suspected vaccine anaphylaxis and record in detail all symptoms and signs when they occur. Signs and symptoms suggestive of anaphylaxis following vaccination should be managed as anaphylaxis and the vaccinee treated with intramuscular adrenaline.

INTRODUCTION

Despite over 6 billion vaccines being administered globally, anaphylaxis is rarely reported by health providers as an adverse event following immunisation (AEFI). Unfortunately, many countries do not have robust surveillance systems for reporting AEFIs but even when one takes this into account, it is likely that vaccine anaphylaxis is rare. Furthermore, in westernised and industrialised countries, despite a recent increase in the incidence of atopic disease and food allergies (predominately nut) and an increase in the number of vaccines administered to young children, there appears to be no increase in the occurrence of vaccine anaphylaxis. Although rare vaccine anaphylaxis remains important because it is one of the very few vaccine reactions that may be life-threatening, vaccine anaphylaxis is treatable and, perhaps most importantly, often misdiagnosed with significant implications for the individual patient.

This review provides an approach to the investigation of a patient who presents, for a clinical review, with suspected vaccine anaphylaxis. Frequently any sudden and severe event following an immunisation is diagnosed and reported as anaphylaxis. In such situations the first step is to ascertain if the reported symptoms and signs do fulfil a case definition for anaphylaxis. This is important both when assessing an individual case and for the purposes of pharmacovigilance. Recent progress has been made, by the Brighton Collaboration (BC), in

formulating case definitions for a number of adverse events following immunisation, including anaphylaxis. The BC is an international group of vaccine safety experts whose brief is to harmonise AEFI case definitions. Not uncommonly, the case definition is not met, and it is important to consider what alternative conditions may have occurred post immunisation. However, if the case definition is met, then an assessment needs to be made as to whether the episode of anaphylaxis was triggered by the vaccine or alternative trigger(s). Prevention of vaccine anaphylaxis is important and if vaccine anaphylaxis is diagnosed, this is a contraindication to the subsequent use of the same vaccine(s). In this situation it is important to consider alternative methods of protection (if available) against vaccine-preventable disease. In a small minority of children with food allergies specific vaccines may be contraindicated or require administration using special precautions.

Prior to providing a clinical approach the reported rates of anaphylaxis and possible mechanisms of anaphylaxis are discussed in further detail.

REPORTED RATES OF VACCINE ANAPHYLAXIS

Anaphylaxis following vaccination is considered to be very rare and the risk is often documented, in immunisation information provided to the public, as 1-2 cases per million vaccine doses.¹ However, it is less clear when one considers the published literature on the reported rates of anaphylaxis following vaccination which varies widely from 0.65 to 120 per million vaccines²⁻⁴ (Brotherton *et al.*'s Table 2 gives a comprehensive summary of reported rates²). This wide variation in the reported rate of anaphylaxis is accounted for by a number of factors but most importantly the ascertainment of cases and the accuracy of denominator data (i.e. the number of vaccine doses administered). The ascertainment of cases will vary according to the method of surveillance (spontaneous reporting or active surveillance) and the case definition which is used. While it would be ideal to use the administered doses of a vaccine as a denominator, such data are seldom available. Often the denominator is estimated from the distributed doses of a vaccine and an estimation of vaccine coverage. It is also likely that factors inherent to the target population which is being vaccinated (e.g. adolescent girls receiving the human papillomavirus vaccine (HPV)) and the inherent composition of a vaccine (e.g. gelatine in measles, mumps, rubella (MMR) vaccine) may also contribute to the variable rates of anaphylaxis. To illustrate these points Bohlke *et al.*⁴ reported an anaphylaxis rate of 0.65 per million vaccines. In this study cases were ascertained within hospitals and according to ICD coding and all vaccines were included (5 cases and 7 644 049 doses). In contrast, Erlewyn-Lajeunesse *et al.*³ calculated a rate of 120 per million vaccines (single component measles vaccine). Cases were reported to the British Paediatric Surveillance Unit using a stimulated method of surveillance, and this analysis included a single component measles vaccine only (2 cases and 16 625 doses). An appreciation of these factors is important when interpreting rates of vaccine anaphylaxis and also highlights the importance of good surveillance data which are specific to the population and vaccines which are used in the community of interest.

MECHANISM OF ANAPHYLAXIS

The mechanism of vaccine anaphylaxis is poorly understood. When the mechanism has been documented to be IgE-mediated the potential allergen is usually one of the residual proteins used in vaccine manufacture rather than one of the vaccine antigens. Kelso *et al.*⁵ were the first to document gelatine allergy in a single patient who presented with anaphylaxis to an MMR vaccine. Gelatine is used as a stabiliser and was most commonly included in live viral vaccines. However, few vaccines now contain gelatine and gelatine allergy is rare in most communities. The majority of influenza vaccines and the yellow fever vaccines are manufactured in embryonated chicken eggs and may contain residual quantities of egg protein and potentially trigger IgE-mediated anaphylaxis. In practice, the vast majority of influenza vaccines contain negligible amounts of egg and are well tolerated in egg-allergic individuals.⁶ Non-IgE-mediated mechanisms of anaphylaxis (so-called anaphylactoid reactions) are likely, and could include complement activation and IgG-mediated anaphylaxis. Understanding this is important when it comes to investigating vaccine anaphylaxis.

CLINICAL APPROACH TO THE INVESTIGATION OF A SUSPECTED CASE OF VACCINE ANAPHYLAXIS

Are the reported symptoms and signs consistent with anaphylaxis?

Sudden and severe events occurring post vaccination are not infrequently reported as anaphylaxis; therefore the first step is to assess if the reported symptoms and signs are consistent with anaphylaxis. While a history from the vaccinee (or parent) is important, all health care provider documentation (e.g. ambulance records, emergency department clinical notes) should be obtained for review. Not infrequently this assessment is compounded by poor documentation of the event. Nevertheless, all symptoms and signs should be documented and then the Brighton Collaboration (see www.brightoncollaboration.org) case definition for anaphylaxis can be used to ascertain if an anaphylaxis case definition is met.⁷ While the primary purpose of the BC case definitions is pharmacovigilance, the BC anaphylaxis case definition has been useful for clinical cases and correlates well with other consensus definitions of anaphylaxis.^{8,9} Education of vaccine providers in AEFI reporting, including documentation of the symptoms and signs that would be helpful to subsequently assign a case definition, should be included in vaccine provider education.¹⁰ An elevated mast-cell tryptase level is included in the case

definition, and potentially this could be helpful, but is rarely considered within a primary care or emergency department setting where children are likely to present post immunisation. Treatment with adrenaline is not included in the case definition as this is not infrequently administered to children with vasovagal events after immunisation.¹¹

Table 1 lists a number of conditions which could be mistaken for vaccine anaphylaxis.

Is the anaphylaxis triggered by the vaccine(s)?

Importantly, the case definition (or levels of certainty) is not an assessment of causality – i.e. was anaphylaxis triggered by the vaccine? This is a separate assessment and should only be considered once the case definition has been met. Clearly, this assessment is based on a number of factors including the temporal relationship between vaccination and the onset of symptoms, the absence of alternative triggers and subsequent demonstration of vaccine sensitisation to the vaccine or vaccine excipient (if an IgE-mediated mechanism). Unlike the investigation of a drug allergy, vaccine rechallenge is seldom feasible in order to demonstrate causality. In one case series ($n=8$) the onset of first symptom ranged from 15 to 120 minutes after immunisation.³ However, when symptoms occur immediately (<1 minute), these are not likely to be due to anaphylaxis and more likely to be due to a vasovagal event caused by injection site pain. Other triggers to be considered include medication administered immediately prior to immunisation and even food allergens in children with known food allergies (e.g. a sweet containing egg given as a treat post immunisation to an egg-allergic child).

Subsequently, investigations including skin-prick and intradermal testing may provide supportive evidence to implicate a specific vaccine. When performing intradermal skin testing most vaccines, and particularly adjuvanted vaccines, are irritating to the skin and require dilution to avoid a high false-positive rate. In general, vaccines should be diluted by 1 in 10 or 100 for intradermal skin testing; recommendations for vaccine dilutions have been published.¹² The positive and negative predictive value of vaccine intradermal testing is not known. Following general principles, a positive skin test (with dilutions) is likely to indicate IgE-mediated sensitisation to a vaccine protein and in the correct clinical context can be supportive of the diagnosis of vaccine anaphylaxis. There is likely to be a significant false-negative predictive value because of non-IgE-mediated mechanisms of anaphylaxis. Nevertheless, in one small study using these principles 18 girls who had skin rash following

Table 1. Conditions that may be mistaken for anaphylaxis post immunisation

Hypotonic hyporesponsive episode	Onset 2-6 hours post immunisation, sudden pallor, hypotonia and unresponsiveness, usually in an infant. No skin rash, respiratory or cardiovascular compromise
Vasovagal event	Symptoms commence during the injection process (i.e. immediate), no skin rash, bradycardia not tachycardia, no respiratory involvement. Spontaneous resolution when prone
Seizure	Sudden unresponsiveness usually with tonic clonic movement, usually febrile, no cardiovascular compromise, no respiratory compromise unless apnoea or aspiration
Aspiration of oral vaccine, e.g. oral polio or rotaviral vaccine	Immediate respiratory symptoms (cough, gagging, stridor or wheeze) during administration, usually in infant. No skin rash or cardiovascular compromise
Somatic conversion symptoms	Immediate or delayed respiratory symptoms, syncope, neurological symptoms without signs
Coincidental diseases	Usually due to coincidental – unrecognised – congenital disease (e.g. heart) or infection
Injection programme error	Immediate toxic drug reaction reported programme error with muscle relaxants or toxic shock

the HPV vaccine and who were negative on intradermal skin testing (1 in 10 dilution) were challenged with an HPV vaccine; only one developed limited and delayed urticaria.¹³

Revaccination and subsequent protection with vaccine anaphylaxis?

Revaccination with the same vaccine antigens or other vaccines containing the same excipients is contraindicated when vaccine anaphylaxis is diagnosed. This should not prevent vaccination with all of the other recommended vaccines, and there is no evidence to support the contention that the risk of anaphylaxis to other vaccines could be elevated. However, often multiple vaccines are administered simultaneously and these contain multiple vaccine antigens and excipients. For example, diphtheria and tetanus antigens are used as protein carriers in the meningococcal C conjugate vaccines and this may have implications in a child who has anaphylaxis following a diphtheria, tetanus and pertussis vaccine (DTP). Therefore, it is important to provide clear and written advice as to which vaccines can be administered. In a few selected diseases and when revaccination is contraindicated, parents should be advised of alternative methods of protection such as erythromycin following pertussis exposure, use of tetanus immune globulin when tetanus is a significant risk and the possible use of acyclovir with Varicella exposure (in the immunocompromised). Desensitisation to vaccines has not been documented.

Can vaccine anaphylaxis be prevented?

A prevaccination checklist should include a question about any serious reactions to previous vaccines including anaphylaxis. Children with a known gelatine allergy should not be given vaccines containing gelatine. More problematic are misconceptions that the MMR vaccine cannot be given to children with an egg allergy (including those with egg anaphylaxis). The MMR vaccine has been shown to be safe in these children.¹⁴ The product information and many immunisation guidelines indicate that influenza vaccine derived from egg culture is contraindicated in children with egg allergy. However, recent case series of influenza vaccination in egg-allergic children have demonstrated that immunisation is safe. For some egg-allergic children (those with egg anaphylaxis), immunisation under specialist medical supervision is recommended. Although these current guidelines are yet to be reflected in the product information, many allergy expert groups have provided immunisation guidelines.^{14,15} The product information for the hepatitis B and HPV vaccines indicates that these vaccines should not be given to children or adolescents with anaphylaxis to baker's yeast (*Saccharomyces cerevisiae*). However, no cases of childhood anaphylaxis, following hepatitis B vaccine, have been described where baker's yeast allergens have been identified as the cause.¹⁶ The vaccines can be given to individuals with an allergy to inhaled yeast (for example *Aspergillus*). Neomycin allergy is listed as a contraindication for some vaccines; however this antibiotic is seldom used and neomycin allergy is rare.

CONCLUSION

Vaccine anaphylaxis is rare and is often misdiagnosed. This is important because a misdiagnosis may preclude an individual from receiving protection from certain vaccines and this may result in a vaccine-preventable illness. For the minority of individuals who do have vaccine anaphylaxis it is important that subsequent immunisation with the implicated vaccines are contraindicated. It is important for all health care providers to report any suspected vaccine anaphylaxis and to record in detail all symptoms and signs when they occur. Any vaccinee who presents with signs and symptoms suggestive of anaphylaxis should be treated with adrenaline as this is safely administered by the intramuscular route.

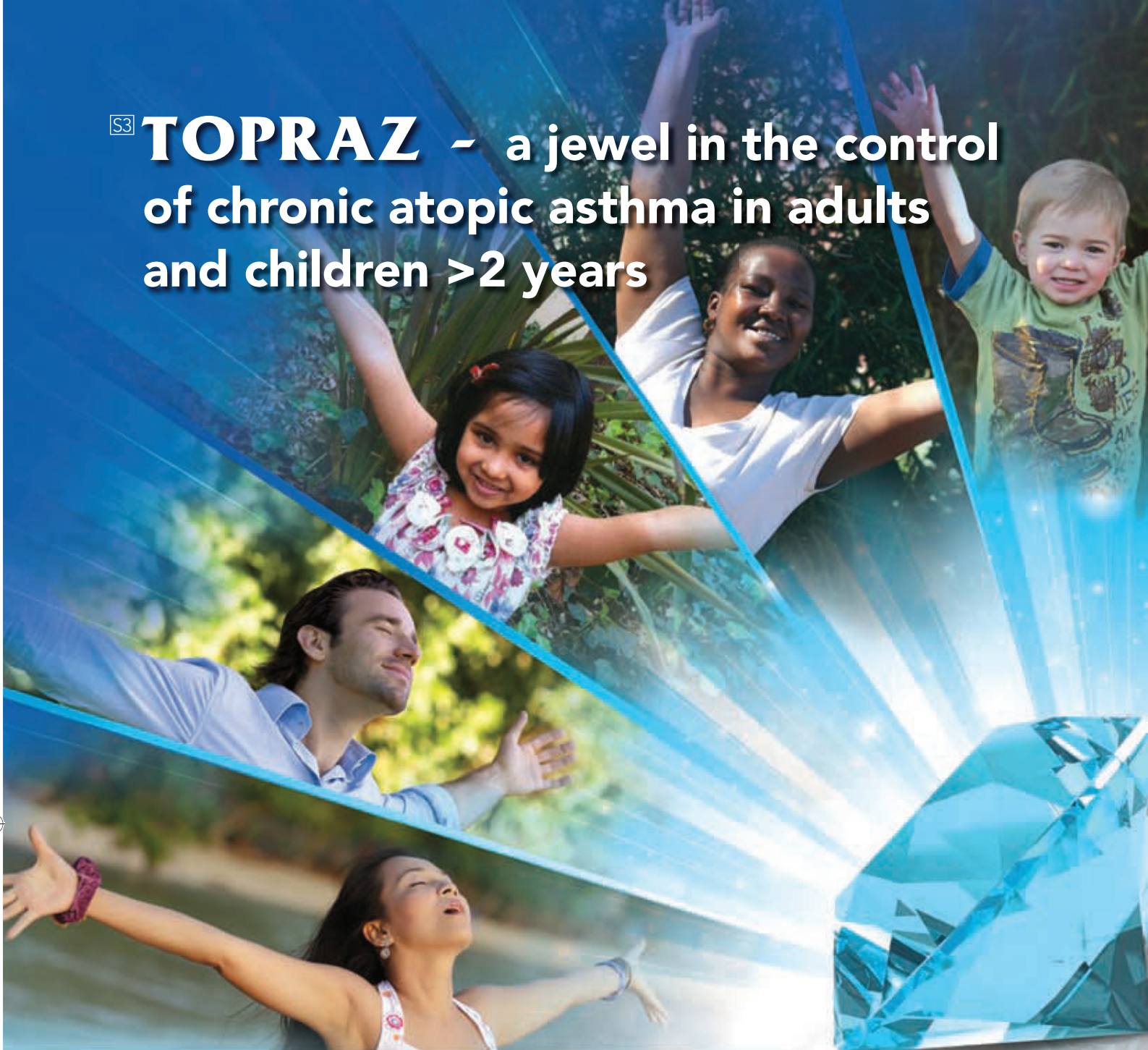
Declaration of conflict of interest

The author declares no conflict of interest.

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