

Prevention of anaphylaxis in healthcare settings

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In this paper, we review recent evidence on preventing anaphylaxis in healthcare settings and contexts where the risk of developing anaphylaxis is known to be increased. These include investigation units in which patients are undergoing challenge testing, outpatient clinics undertaking immunotherapy and vaccination, inpatient settings in which patients receive antibiotics, non-steroidal anti-inflammatory drugs, opiates and biological agents and operating theatres in which patients receive general anesthetics. Anaphylaxis may however develop unpredictably in any patient exposed to a wide range of drugs, food and other triggers (e.g., latex, iodinated contrast media and exercise), so it is important that all healthcare professionals and systems have effective, well-rehearsed protocols for risk assessment and management of this allergic emergency. Where available, we consider evidence for the effectiveness of interventions aiming to reduce the risk of developing anaphylaxis.

KEYWORDS: anaphylaxis • emergency • guidelines • management • patient safety • prevention

Key conceptual considerations

Defining anaphylaxis

Anaphylaxis has been defined as ‘a serious, life-threatening generalized or systemic hypersensitivity reaction’ [1]; it is typically rapid in onset and may cause death [2]. It is characterized by rapidly developing, life-threatening airway and/or breathing and/or circulation problems usually associated with skin and mucosal changes [2,3]. A number of organ systems may be affected resulting in a range of clinical features, including: pruritus, erythema, urticaria, angioedema/facial edema; abdominal pain, nausea/vomiting and diarrhea; rhinitis and sneezing; hoarseness, cough, dyspnea (bronchospasm, laryngeal edema) and respiratory arrest; hypotension, arrhythmias, chest pain and cardiac arrest [3,4].

The recent World Allergy Organization anaphylaxis guidelines [1] suggest the following clinical criteria for diagnosing anaphylaxis (Box 1).

Anaphylaxis most commonly results from an IgE-mediated reaction in which the allergen (s) bind with allergen-specific IgE bound to high affinity IgE receptors on mast cells and basophils to trigger release of an array of inflammatory mediators. IgE-independent mechanisms are, however, responsible for a

proportion of episodes of anaphylaxis, particularly in adults [1].

Insights from epidemiological studies

Reliably estimating the incidence of anaphylaxis is challenging because this needs large population-based cohort studies of people followed over long periods of time. The lifetime prevalence of anaphylaxis has been estimated at 0.05–2%, but this may be an underestimate, due to uncertainties regarding the definition of anaphylaxis, accuracy of recognition and diagnosis and incomplete case reporting [1,5].

The available epidemiological evidence has revealed that anaphylaxis can affect males and females of any age, ethnic and socioeconomic group, with or without any prior history of allergy or anaphylaxis. The key implication of this observation for health system planners and healthcare professionals is that any patient is potentially at risk of experiencing anaphylaxis [6]. Certain sub-populations are however at higher risk, in particular, those who have had previous episodes of anaphylaxis. Furthermore, certain procedures carry inherent risks, for example, food and drug challenges, vaccinations and the administration of anesthetics. In order to reduce iatrogenic morbidity and mortality, health systems therefore need protocols for risk assessment and the emergency management of anaphylaxis.

Box 1. World Allergy Organization clinical criteria for diagnosing anaphylaxis.

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g., generalized urticaria, itching or flushing, swollen lips-tongue-uvula) and at least one of the following:
 - A) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - B) Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia (collapse), syncope, incontinence) OR
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours)
 - A) Involvement of the skin-mucosal tissue (e.g., generalized urticaria, itch-flush, swollen lips-tongue-uvula)
 - B) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - C) Reduced blood pressure or associated symptoms (e.g., hypotonia (collapse), syncope, incontinence)
 - D) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting) OR
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours)
 - A) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure
 - B) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF: Peak expiratory function.

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Prevention

The concept of prevention has been given a good deal of attention by epidemiologists and public health physicians. A commonly used approach is to consider primary, secondary, tertiary and quaternary prevention (see Box 2). For the purposes of this paper, we focus on evidence in relation to primary prevention (i.e., preventing incident episodes) and tertiary prevention (i.e., trying to reduce risk of recurrence in those who have previously experienced anaphylaxis).

Challenges in developing a secure evidence base to inform prevention considerations

The existing evidence base regarding the epidemiology (i.e., frequency, risk factors and outcomes), prevention considerations and management of anaphylaxis is generally limited. Primary prevention, by definition, involves intervening in those who do not yet have the disease. The burden of proof required to recommend any intervention should therefore be very high since any intervention can introduce new risks; primary prevention trials are usually informed by a detailed appreciation of risk factors, but given the limited epidemiological evidence, this is understandably challenging. These studies also typically need to be very large, particularly in the case of anaphylaxis because of its low incidence. Undertaking rigorous primary prevention studies is therefore a complex

and costly undertaking, which may explain the lack of available evidence. While still small and methodologically weak, there is in contrast a growing evidence base in relation to tertiary prevention considerations.

In writing this review, we preferentially draw on systematic reviews and randomized controlled trials (RCTs), but where these are unavailable we consider evidence from other less rigorous study designs to consider how best to minimize the risk of patients developing either a first or repeat episode of anaphylaxis. We review evidence on preventive strategies for each specific trigger and then outline general approaches to prevention of anaphylaxis in healthcare settings.

Health contexts & healthcare settings associated with increased risk of anaphylaxis

Although all patients are potentially at risk in any clinical setting, particular procedures and agents carry an increased risk of triggering anaphylaxis. Of particular interest are the factors implicated in fatal episodes. A major UK review of 164 fatal anaphylaxis reactions during the period 1992–1998 found that almost half were iatrogenic [7]. Anesthetic agents, antibiotics and contrast media were particularly implicated, with nonsteroidal anti-inflammatory drugs (NSAIDs) angiotensin-converting-enzyme (ACE) inhibitors and a range of other drugs also responsible for some fatalities. Each year in the UK, it is estimated that at least nine deaths from anaphylaxis can be attributed to pharmaceuticals [8]. These are the best European data available, but a systematic review on the epidemiology of anaphylaxis in Europe is in progress [9]. A recent review of anaphylaxis deaths in Maryland, USA suggested that 5/17 (29%) of deaths were drug-related, but this is likely to be an underestimate [10]. An Australian review identified 22/112 (20%) of anaphylaxis fatalities between 1997 and 2005 as drug-related [11]. The number of non-fatal reactions is poorly documented.

Changing patterns of drug use in anesthesia and the community, changes in the use of substances such as latex and iodinated contrast media, and the introduction of new

Box 2. Levels of prevention.

Primary prevention: Preventing the onset of anaphylaxis

Secondary prevention: This relates to screening to identify pre-clinical disease; this is not really directly relevant to anaphylaxis, but may by extension be used to identify risk factors, e.g., atopy and mastocytosis

Tertiary prevention: Reducing risk of recurrence and improving outcomes in those with a history of anaphylaxis

Quaternary prevention: System changes to try and reduce the risk of individuals developing anaphylaxis, e.g., protocols for avoiding unnecessary antibiotic prescribing

treatments, such as monoclonal antibodies (mAbs), mean the epidemiological picture is constantly changing [12,13]. For example, anaphylaxis related to antibiotics appears to be increasing [12], this possibly reflecting the increasing prevalence of allergy to these drugs in the general population as well as their increased use in perioperative prophylaxis. By contrast, the reduced use of latex in healthcare settings (e.g., by changes in the manufacturing process and reduced use of latex gloves) appears to have led to a decline in latex-triggered anaphylaxis [14].

Identification of relevant allergic triggers can prove challenging, particularly in the context of drug-induced reactions. The most important step in securing a diagnosis is the taking of a comprehensive history, which then serves to guide the requesting and interpretation of diagnostic testing. Thus, diagnosis is made on the basis of detailed history based on the criteria in Box 1, examination and *in vitro* and/or *in vivo* allergy tests (including challenge testing where necessary) to confirm or refute the diagnosis [1].

Contexts/procedures associated with increased risk of anaphylaxis

For contexts/procedures associated with increased risk of anaphylaxis, refer to Box 3.

Investigative procedures

Skin prick & prick-prick tests

These can be used to help diagnose IgE-mediated hypersensitivity to allergens and are, if appropriately performed, regarded as useful diagnostic procedures. They are safe procedures in the context of testing to aeroallergens, but there is a small increased risk of triggering a systemic reaction in the context of testing to foods and drugs. This risk has been estimated as less than 0.02% [15]. The remote risk of anaphylaxis caused by skin prick test (SPT) can be mitigated by taking precautions with patients with a history of asthma and/or previous systemic/anaphylactic reactions and, as with all patients where there is any risk of anaphylaxis, staff must have the necessary training, equipment and treatments available to deal with any allergic reaction [15].

Intradermal & patch tests

Intradermal skin tests can be useful in the context of testing for venom and drug allergy, particularly when SPTs are negative [16]. Patch testing is a standardized, *in vivo* diagnostic test used to investigate allergic contact dermatitis and this test is also sometimes used for the diagnosis of food allergy [17,18]. There are occasional case reports of anaphylaxis deaths from both procedures.

Challenge tests

Challenge testing, for example, to foods and drugs, is a common procedure in specialist allergy care settings to confirm/exclude diagnosis and, particularly in the context of food allergy in children, to look for evidence of resolution of food

Box 3. Summary of healthcare contexts/procedures associated with increased risk of anaphylaxis.

Investigative procedures

Skin prick and prick-prick tests, particularly when testing to foods

Intradermal and patch tests

Challenge testing, e.g., to foods, drugs

Radio-contrast media-based diagnostic tests

Procedures using latex gloves/equipment, disinfectants and blue dyes

Interventions

Pharmacological agents: analgesics, antibiotics, chemotherapy, anesthetics

Biological agents: vaccinations, fluids/blood products, monoclonal antibodies

Immunotherapy/desensitization

allergy. The procedure involves giving individuals gradually increasing amounts of the allergen they are suspected/confirmed to be allergic to in order to assess whether this can be safely tolerated. The risk of triggering a reaction – including anaphylaxis – is therefore high, particularly in certain patients/circumstances. In suspected drug allergy, challenge with specific drugs is only recommended after other possible investigations have been exhausted without reaching a conclusive diagnosis [19].

A recent convincing anaphylactic reaction to a trigger, confounding medical conditions (particularly unstable asthma) or medications (such as β -blockers) may be considered as contraindications to challenge testing unless there are compelling reasons to undertake the procedure [20]. Because of the inherent risk, challenges must be conducted at a specialist center with onsite medical supervision and appropriate rescue medication and equipment available [19,21]. The use of slow up-dosing protocols for challenges should minimize the risk of anaphylaxis, that is, the allergen is introduced in small amounts over time, with dose reduction in the event of a severe allergic reaction and/or inter-current illness, as opposed to rush protocols where doses are increased more rapidly [20,22].

Radiocontrast-based diagnostic tests

Radiocontrast media (RCM), used for the diagnosis and treatment of vascular disease and enhancement of radiographic contrast, have, in the past, been a common cause of mild adverse reactions. Fatal hypersensitivity reactions occur in 1–3 per 100,000 contrast media administrations to ionic and non-ionic preparations [23]. It is estimated that about 70% of RCM-induced anaphylaxis occurs within 5 min of injection, and 96% of severe or fatal reactions manifest within 20 min [23]. Modern, non-ionic RCM are relatively safe, with only 0.02–0.04% of procedures resulting in severe immediate adverse reactions, but ionic preparations are still used in some countries as they are less costly.

Patients who have experienced a previous immediate hypersensitivity reaction to an RCM should not be given the same substance in further examinations. SPTs, intradermal tests and

patch tests can be undertaken to investigate RCM allergy [24]. RCMs should, if possible, be avoided in future investigative procedures in those who test positive. In those patients who fail to show evidence of sensitization, a negative skin test does not guarantee that future procedures will be safe; however, the overall risk of a repeat reaction appears to be very low [24].

Although evidence for the effectiveness of premedication is disputed in the general population, it may be considered in patients identified as being at increased risk of anaphylaxis to RCM. This includes patients with a previous history of severe allergic reaction to RCM, a history of systemic allergic reactions and asthma [25–27]. A recent study concluded that screening patients through RCM skin testing is of no clinical utility in predicting hypersensitivity reactions, but may be of ‘modest’ value in retrospectively evaluating severe adverse reactions [28]. A systematic review of the use of medication for prevention of anaphylactic reactions to iodinated contrast media concluded that H1 antihistamines given immediately prior to the administration of ionic contrast may be useful in preventing reactions and glucocorticosteroids may have a protective effect when given in two doses at least 6 h prior and again 2 h prior to the administration of contrast, both ionic and non-ionic. The authors suggest that these agents should be considered for prophylactic use in patients who are at high risk of anaphylaxis to contrast media, that is, those who have had previous reactions to contrast media and patients with asthma. However, the limited number of high-quality RCTs addressing optimal methods to prevent allergic reactions to contrast media means the recommendation can only be made with caution [29]. A further review of both antihistamines and glucocorticosteroids challenged their use as premedication in patients at high risk for immediate RCM reactions [30]. The authors point out that severe reactions still may develop in patients who receive premedication and conclude that in unselected patients, the usefulness of premedication is doubtful and its routine use should be abandoned [30].

Procedures involving latex, chlorhexidine/disinfectants & blue dyes

Latex is employed in the manufacture of many items ubiquitous in healthcare settings, such as gloves, catheters, syringes, tubing, dressings, masks and cannulas, and 14 different latex allergens have been identified [31]. Latex provides an educative case study regarding the recognition of new allergens and the effectiveness of preventive measures.

Latex is the second most common trigger of perioperative anaphylaxis after neuromuscular blocking agents (NMBAs). The frequency of perioperative anaphylaxis attributed to latex has remained relatively stable in recent years, estimated at between 12 and 20% of perioperative anaphylaxis cases [13,31,32]. Reactions to latex normally occur during the maintenance phase of anesthesia, unlike anaphylaxis due to muscle relaxants and opiates, which is more frequent in the induction phase. Abdominal, gynecological and orthopedic operations present the greatest risk [31].

In children, it has been estimated that latex is involved in 27% of anaphylactic reactions associated with anesthesia, with higher figures in the under-fives and children with spina bifida [31,33]. The risk of anaphylaxis to latex appears to be greater in atopic individuals and for those with higher levels of exposure, for example, patients undergoing multiple operations or tests, or people with occupational exposure to latex. Patients with clinical manifestations of allergy to tropical fruits (e.g., avocado, banana, kiwi, pineapple, papaya) should be considered at risk because of the high rate of cross-reactivity with latex (also sometimes known as latex–fruit syndrome) [13,14,31].

Measures to reduce the protein content of latex in gloves, reducing the powder in gloves, the availability of alternative substances to manufacture gloves and prevention strategies have helped to reduce the risk to patients, but the international picture indicates considerable variation in exposure, with an anticipated increase in incidence in newly industrialized countries; non-latex gloves, for example, are more expensive than latex ones [14,31]. Children with spina bifida are particularly at risk and the sooner spina bifida can be identified (*in utero* or soon after birth), the sooner primary prevention, that is, rigorous latex avoidance measures, can be commenced [14].

Labeling of products to facilitate avoidance is supported by legislation, for example, packaging of latex gloves must be labeled ‘Contains latex from natural rubber, which may cause allergic reactions’. Clear protocols should exist in all hospitals for procedures to follow when treating a latex-allergic patient. Preparation of operating theatres for those who are latex allergic is addressed by guidelines [13]. These include: preparation of the operating theatre the night before surgery to avoid the release of latex particles; scheduling the latex-allergic patient first on the list; placing a ‘Latex allergy’ notice on the doors to the anesthetic room and operating theatre; limiting staff traffic; absolute use of synthetic gloves/latex-free products when preparing equipment and during anesthesia, surgery and postoperative care; removing non-essential equipment from the vicinity of the patient; recording latex allergy in the case-notes, on the patient’s wrist band and ensuring that the entire surgical and post-operative care teams are informed of the allergy. The authors also suggest that the use of antihistamines and glucocorticosteroids for premedication is inconclusive; this is reviewed in more detail below.

Chlorhexidine & other commonly used disinfectants

The increasing use of chlorhexidine as an antiseptic preparation and its use in other products such as catheters may result in increased incidence of sensitization and anaphylaxis. [34,35]. The true incidence is unknown, but based on case reports, may be increasing [34,36]. Beaudouin *et al.* identified 50 reported cases of chlorhexidine anaphylaxis in 10 years, 15 occurring during surgery [37]. Severe allergic reactions to chlorhexidine may occur in patients who have previously experienced mild reactions [38]. Where previous anaphylaxis in a healthcare setting has an unidentified cause, clinicians should have a high index of suspicion regarding chlorhexidine and enquire if it was used or was

impregnated in any medical equipment used, as it may be overlooked as a causative agent; it can if necessary be replaced with other disinfectants [34,39]. There are also case reports of anaphylaxis to povidone-iodine [40,41]. SPTs and specific IgE tests can confirm the diagnosis of both chlorhexidine and povidone-iodine allergy; avoidance is however challenging due to the ubiquity of both substances in a wide range of products within healthcare settings and beyond [35,40,42].

Blue dye

Case reports suggest that blue dyes, such as Patent Blue V and isosulfan blue, increasingly used for lymphatic mapping during surgery, are associated with anaphylaxis [35,43,201]. Recommendations for practice merely suggest the need for raised awareness of the potential for anaphylaxis and avoiding the use of blue dyes in patients with a history of allergy to foods containing food colorant E131, or with a history of anaphylaxis requiring them to carry self-administered epinephrine [43].

Interventions

Pharmacological agents

The true incidence of anaphylaxis to drugs is unknown, but β -lactams, NMBAs, aspirin/ NSAIDs, local anesthetics and opiates are the most commonly implicated drugs. Tests are unavailable for many drugs, therefore specialist expertise in diagnosis and management of drug allergy is essential [19].

Analgesics

NSAIDs are commonly used medications with known risks of hypersensitivity reactions, including anaphylaxis [44,45]. Opioids can result in direct mast cell degranulation and result in anaphylaxis, but this is rare [46]. Preventive strategies in a single-drug reaction should focus on identifying safe alternative drugs, preferably from a structurally different class of agents (TABLE 1) [47]. Patients who react to aspirin may also react to other NSAIDs, this in many cases being mediated through blockade of the enzyme COX-1 [47].

Antibiotics

While reported allergy to penicillins is common, confirmed diagnosis is rare, partly due to the limited availability and accuracy of testing and ethical concerns about the risks associated with challenge testing, particularly in children; overdiagnosis is therefore likely [19]. Anaphylaxis related to antibiotics is mainly due to penicillins and there is some cross-reactivity with cephalosporins. A recent literature review suggested that this is less common than previously thought: in patients with a history of penicillin allergy who were given a cephalosporin, cross-reactivity between penicillins and most second- and all third- and fourth-generation cephalosporins was negligible [48]. The authors concluded that in patients who have had an allergic response to penicillin, it is safe to administer a cephalosporin with an R1 side chain that is structurally dissimilar to that of the penicillin or to administer a third- or fourth-generation cephalosporin. A recent systematic review of four prospective

studies of penicillin-allergic patients who were then skin tested with a carbapenem identified the reported incidence of cross-reactivity between penicillins and carbapenems as about 1%, that is, much less than previously thought [49]. The same review concluded that monobactams are less safe in penicillin-allergic patients than previously thought, with some indication of cross-reactivity, although other reviews suggest there is no cross-reactivity between monobactams and penicillins [50,51]. Patients with severe penicillin allergy should therefore not be given β -lactam antibiotics unless a careful risk–benefit assessment indicates otherwise [50,52].

Reducing exposure where possible for those with proven or a strongly suspected history of anaphylaxis is essential, for example, by limiting unnecessary prescribing of antibiotics and identifying safe alternative drugs. The risk of severe reactions and anaphylaxis seems to be enhanced with parenteral use of antibiotics, evidenced by the rapidity of symptom onset [53,54]; although head-to-head trial-based evidence is lacking, it may be safer to give oral treatment unless there is a very good reason to use intramuscular or intravenous treatment. Patients with cystic fibrosis have higher prevalence of anaphylaxis to antibiotics, thought to be due in part to frequent and repeated exposures. Rapid desensitization protocols have been developed and are commonly used in this patient group (see section on desensitization to drugs) [45].

Chemotherapies

Acute drug hypersensitivity reactions to chemotherapeutics are infrequent and usually mild, but the most likely agents to cause anaphylaxis are platinum compounds, taxanes, L-asparaginase, epipodophyllotoxins and procarbazine [55]. The most severe reactions usually occur within minutes of exposure, although delayed reactions 10–12 h after exposure are possible [55]. A retrospective review of case notes in a US cancer center examined records of 300,850 infusions in 4000 patients between 2006 and 2010 and found the incidence of acute hypersensitivity reactions was 0.7% (222 cases). Immunotherapeutics were responsible for half of all hypersensitivity reactions, with rituximab accounting for 54% of these [55].

Preventive strategies in oncology units focus on premedication protocols, which recommend giving specific drugs such as paracetamol or glucocorticosteroid plus an antihistamine prior to administration of anticancer drugs [55]. However, such protocols appear to be ineffective in preventing anaphylaxis. Desensitization and re-challenge may be possible for less severe hypersensitivity reactions to chemotherapeutic and immunotherapeutic agents, reducing the rate from up to 40 to 10% among patients receiving paclitaxel infusions, for example [56], although it has been questioned whether desensitization is effective when anaphylaxis has occurred [55]. In addition, interventions to limit hypersensitivity reactions by administering premedication, slowing infusion rates or both are not always successful, and may lead to permanent discontinuation of the medication, compromising effective treatment [56].

Anesthetics

Mertes *et al.* describe the anesthetic setting as 'a pharmacologically unique situation', where patients are exposed to multiple agents with the potential to trigger anaphylaxis [35]. These substances include anesthetics, analgesics, antibiotics, antiseptics, blood products, heparin, polypeptides and intravascular volume expanders. These often multiple exposures also create difficulties in isolating the causative agent in anaphylaxis, particularly if latex, dyes and contrast media are also used.

The incidence of anaphylaxis during anesthesia has been estimated between 1 in 10,000 and 1 in 20,000 general anesthetics [13,57]. A study of three French databases estimated the incidence of allergic reactions to anesthetics at 100.6 (76.2–125.3) per million procedures, with NMBAs the most frequently implicated substances, followed by latex and antibiotics, mainly penicillins and cephalosporins [46]. Allergy to hypnotic agents, opioids, colloids, aprotinin and protamine are less frequent and allergy to local anesthetics appears to be very uncommon [35].

Certain factors associated with an increased risk of anaphylaxis have been identified, indicating where good pre-operative risk assessment might raise awareness of potential preventive measures. Patients with a history of atopy, asthma or food allergy appear to be at greater risk of latex allergy, but not anaphylaxis to NMBAs or antibiotics [13]. Patients with asthma or taking β -blocking drugs may experience more severe reactions [13]. The marked international difference in the prevalence of anaphylaxis to NMBAs indicates that environmental influences may be important. A recent Scandinavian survey identified exposure to pholcodine, an ingredient of cough syrup which is available without prescription in Norway, as a factor in the greater incidence of NMBA anaphylaxis compared with Sweden [13,58].

Patients who have previously experienced anaphylaxis under anesthetic should be investigated to try to determine the cause of the reaction and targeted for preventive measures if they require a further anesthetic. The ideal scenario includes serial measurement of serum tryptase levels, specialist allergist follow-up, testing for sensitivity to relevant suspected drugs or other products patients may have been exposed to, such as latex, to identify the cause of anaphylaxis, and identification of a safe alternative drug or product [13,13,59]. There are, however, limitations, for example, this can only be conducted where surgery is elective, where specialist allergy services exist and where validated tests are available: this is not the case for certain drugs including NSAIDs [12,59]. The sensitivity and specificity of skin tests and blood tests is relatively low. Unless there is a positive history of previous anaphylaxis, neither a negative test nor a positive test is likely to be predictive of outcome [13].

Screening all patients prior to anesthesia is not recommended, due to the relatively low risk of anaphylaxis in the general population. Allergy testing in patients who are atopic without having any other risk factor for sensitivity to relevant agents is not recommended [12]. Test dosing with suspected trigger allergens, for example, by giving an intravenous antibiotic, is not recommended [13]. According to Dewachter and

Hepner, no prospective randomized study evaluating the use of a specific protocol of premedication on the prevention of perioperative anaphylaxis has been published [60]. Nonetheless, routine use of premedication appears to have clinical support [33].

The UK guidelines on suspected anaphylaxis during an anesthetic recommend collaboration between a specialist allergist, who can best interpret investigation results, and an anesthetist, who can recognize possible non-allergic causes for any reaction [13]. Reporting on follow-up of patients who had experienced anaphylaxis under anesthetic in Australia, Fisher *et al.* suggest that subsequent anesthetics in patients for whom no cause was identified are usually safe, with 51 out of 52 patients they followed-up having subsequent uneventful anesthesia. Of 301 patients with a cause found for their anaphylaxis, 295 had uneventful anesthesia and 6 had a second reaction [61]. This suggests that prevention can, in some cases, be effective, provided the trigger can be identified and an alternative agent found. Fisher and Doig suggest that preventing subsequent anaphylaxis requires conducting appropriate investigations, communicating the results of these to the patient and anesthetist, avoiding high-risk drugs such as suxamethonium chloride and, in those at highest risk, considering pre-treatment and desensitization [62].

Biological agents

Vaccinations

Anaphylaxis is a known, but rare event following vaccination, although the public perception may be that it is more common than the evidence suggests [63]. Anaphylaxis is thought to occur at a frequency of between 1 and 10 cases per million doses of vaccine given [202]. A recent evidence reviewed by the Institute of Medicine in the USA concluded that the evidence 'convincingly supports' that six types of vaccines—measles, mumps and rubella (MMR), varicella zoster, influenza, hepatitis B, meningococcal and tetanus-containing vaccines are linked to anaphylaxis [64]. A recent survey of clinicians reporting adverse events following immunization in children under the age of 16 years estimated the incidence as 12.0 per 100,000 doses for single component measles vaccine and 1.4 cases per million doses for the bivalent human papilloma virus vaccine [65]. There were no cases in pre-school children and infants, despite over 5.5 million vaccinations being given, including MMR and influenza vaccines. Vaccines are a mixture of compounds, and hypersensitivity reactions can occur to any component, including the vaccine antigen, an adjuvant such as alum or yeast, binding substances used in the manufacturing process such as ovalbumin, gelatin and neomycin, or to the latex stopper on the vial [65,66].

Preventive strategies are mainly of value where risks are known, therefore any history of egg, drug or latex allergy should be identified prior to administration [66]. It is recommended that children with idiopathic anaphylaxis are immunized in a center accustomed to treating anaphylaxis and are observed for at least an hour following administration [65]. Both skin testing and testing for specific IgE antibodies in serum have been used

for the diagnosis of allergic reactions related to MMR, influenza, DTP, varicella and pneumococcal polysaccharide vaccines, as well as for the diagnosis of reactions to components such as egg and gelatin, but the sensitivity and specificity of these tests for vaccine allergy have not been determined [66]. Guidelines for subsequent immunization following an allergic adverse event are available, including an algorithm for assessing clinical decision-making [66]. Re-immunization following anaphylaxis should be assessed and conducted only in specialist allergy centers, using alternative preparations if available and using a dose-escalating protocol to administer the vaccine [65,66].

The UK guidelines on administering vaccines to egg-allergic individuals state that three vaccines are cultured on derivatives of hen's eggs (MMR, influenza and yellow fever). The MMR vaccine contains a negligible amount of egg protein and is considered safe for egg-allergic children. However, influenza and yellow fever vaccines contain measurable amounts of egg protein, and although the risk of anaphylaxis is low, some precautions are recommended [67,68]. The most recent UK guidelines (2013) suggest that patients with a confirmed history of anaphylaxis to egg or egg allergy with uncontrolled asthma can be immunized with egg-free influenza vaccine, if available, as a single dose in primary care. If no egg-free vaccine is available, patients should be referred to specialists for vaccination in hospital using vaccine with an ovalbumin content less than 0.12 µg/ml. Egg-allergic individuals without confirmed anaphylaxis can be given egg-free vaccine or influenza vaccine with an ovalbumin content less than 0.12 µg/ml as a single dose in primary care. Children aged under 13 years who have not been previously vaccinated should receive the vaccination in two doses. Vaccines with ovalbumin content more than 0.12 µg/ml or where content is not stated should not be used for people with egg allergy [203].

The recent US guidelines on vaccinations recommend that influenza vaccine is given to egg allergic patients, usually in a single dose. Those with a history of anaphylaxis to egg should be assessed by a specialist allergist, but this should not delay vaccination. Those with a proven allergy to the influenza vaccine (i.e., positive skin test to the vaccine or its ingredients) may receive the vaccine in divided doses or have it withheld [68].

Fluids/blood products

Allergic transfusion reactions are the most common complication of blood transfusion. Estimated incidence ranges from 1 to 3% of all transfusions, although this may be a significant underestimate, with up to 10% being suggested [69,70]. The estimated frequency of severe allergic transfusion reactions including anaphylaxis is 7.7% of allergic reactions, or 1.3% of all transfusion reactions [71]. Transfusions with platelets are apparently associated with a higher risk than those with other components, but the etiology and the influence of recipient characteristics are poorly understood [71,72].

Acetaminophen, an antipyretic, and diphenhydramine, an antihistaminic, are widely used as pre-transfusion medications

to prevent transfusion reactions, despite the lack of evidence regarding their effectiveness for this purpose [72]. A recent systematic review of three trials including 462 patients found no evidence that pre-transfusion medication (paracetamol, alone or in combination with diphenhydramine) or hydrocortisone (glucocorticoid) reduces allergic reactions [71]. Platelet reduction has been shown to be effective for preventing allergic transfusion reactions, but washing procedures result in substantial loss of platelets, and the therapeutic effect may be compromised compared with unwashed platelets [72]. In patients with a previous history of anaphylaxis to blood transfusion, slow transfusion, close patient observation and access to trained staff who can administer emergency rescue measures is recommended [70].

Monoclonal antibodies

mAbs are increasingly used in targeted therapy for autoimmune diseases and cancer, with as many as 150 products undergoing clinical trials [73]. A recent systematic review of adverse infusion reactions from mAbs for colorectal cancer found that the incidence varied among different mAbs, with severe reactions ranging from 0 to 22%, compared with 0 to 15% for chemotherapies [74]. Another recent expert review addressed acute infusion reactions, including anaphylaxis, caused by mAbs, highlighting their structural immunogenicity, consequently the immune system may produce specific anti-mAb antibodies that can influence their efficacy [75]. Risk factors for mAb-induced anaphylaxis are as yet poorly characterized, with a lack of RCTs, but there are indications that the nature of the individual patient's disease, the state of their immune system and other medications they are receiving may play a part in causing and preventing severe hypersensitivity reactions [75]. A further expert review addressed desensitization methods for mAb therapy as a means of overcoming the barrier to this potentially highly effective therapy in patients with a history of severe adverse reactions and a lack of equally effective therapeutic alternatives, concluding that desensitization to mAbs leads to significant attenuation of moderate and severe reactions [76].

Omalizumab, an anti-IgE recombinant humanized mAb that decreases the concentration of IgE antibody, was approved by the US FDA in 2003 for treatment of patients aged 12 years and older with moderate to severe persistent asthma with an allergic component whose disease is inadequately controlled with glucocorticosteroids. Treatment with omalizumab has been demonstrated to improve asthma control by reducing the number of asthma exacerbations and improving daytime and nocturnal symptoms [77]. Currently, omalizumab (marketed as Xolair) is the only mAb-based drug approved for the treatment of asthma, but it is not approved by NICE for use in the UK with children. Omalizumab must be administered in a hospital setting due to anaphylaxis risk, estimated at 0.2%.

Of particular relevance to this review is another role for omalizumab, as a means of reducing the risk of anaphylaxis in patients receiving allergen immunotherapy; this is discussed in the next section.

Immunotherapy/desensitization

Allergen-specific immunotherapy may be used for the treatment of allergic rhinitis, allergic asthma, food allergy and venom allergy, aiming to produce immunomodulation and achieving long-term tolerance. Anaphylaxis due to immunotherapy is probably not completely preventable, due to the inherent risk of administering an allergen to an individual who is sensitized to it [78]. The potential for inducing anaphylaxis has limited the use of immunotherapy, especially in patients with severe asthma, who are at greater risk for severe reactions [78,79].

The frequency and severity of side effects may be reduced by careful patient assessment and monitoring, not using rush protocols, and by extending escalation or maintenance phases [78,80,81]. Although direct evidence is lacking, it has been suggested that pre-administration of antihistamines prior to subcutaneous immunotherapy can decrease systemic reactions and may make patients more comfortable during their desensitization procedure [82]. However, there are no recent trials of H1- and H2-antihistamines and/or glucocorticosteroid pre-medication for immunotherapy and their use is not recommended [25,83].

A number of trials since 2002 have indicated that omalizumab used in combination with specific immunotherapy appears to increase the efficacy of immunotherapy and reduce the risk of anaphylaxis [79,84,85]. For immunotherapy patients with severe disease and high allergen-specific IgE, inclusion of anti-IgE mAbs may therefore be useful [81]. A recent multicenter, double-blind, parallel-group study randomized 248 patients (mean age 38.2 ± 9.93) with inadequately controlled asthma to treatment with omalizumab ($n = 126$) or placebo ($n = 122$), prior to receiving specific immunotherapy to at least one of three perennial aeroallergens (cat, dog and house dust mite). Patients receiving omalizumab experienced significantly fewer systemic allergic reactions to immunotherapy than the placebo group (17/126 (13.5%) vs 32/122 (26.2%); $p = 0.017$; 95% CI: 2.91–22.56%) and had fewer respiratory-related systemic allergic reactions (6 vs 24, respectively). Cardiovascular reactions were reported in two patients in each group. More patients pre-treated with omalizumab were able to reach the target maintenance immunotherapy dose (110 (87.3%) vs 88 (72.1%), respectively; $p = 0.004$) [77].

A small pilot Phase I study in 11 children (7–17 years) with cow's milk allergy used omalizumab for 9 weeks prior to rush oral desensitization with milk. No subjects experienced anaphylaxis or adverse reactions which failed to respond rapidly to treatment. The findings indicate that omalizumab may allow rapid milk dose escalation in the majority of subjects, although further placebo-controlled trials are required [86]. Case reports also indicate the potential value of omalizumab in reducing adverse events from antivenom immunotherapy, but no clinical trial data exist [87,88].

These findings suggest that omalizumab, in those countries where its use is approved, may open the door for immunotherapy use in patients with allergic asthma whose symptoms are

inadequately controlled but for whom immunotherapy is not recommended because of an increased risk of anaphylaxis.

Desensitization to drugs

For anaphylaxis to a drug, prevention of recurrence involves substitution of a safe effective non-cross-reacting agent, preferably from a different pharmacological class. If such an agent is not available, desensitization to the implicated agent is indicated to induce temporary clinical tolerance for one uninterrupted course of treatment with that agent [89]. Desensitization to drugs involves the induction of temporary clinical unresponsiveness to drug antigens which have been identified as causing severe hypersensitivity reactions and is typically achieved by gradually giving small doses of drug antigens at fixed time intervals [90]. Rapid desensitization protocols for achieving temporary tolerance to drug allergens, taking 4–8 h, have been developed and found to be safe and effective for both IgE-mediated and non-IgE-mediated severe hypersensitivity reactions to chemotherapy [56]. These allow patients to receive chemotherapy, antibiotics or mAbs, as well as other drugs such as insulin, aspirin and iron. Desensitization is, however, a high-risk intervention in itself [90]. Drugs requiring dosing intervals greater than 24 h, such as chemotherapy and mAbs, need to be administered by desensitization in sensitized individuals with each treatment [45]. Detailed protocols for drug desensitization are available in a range of healthcare contexts [45,56,91].

Antibiotic desensitization in cystic fibrosis (CF) patients has been limited by above average severe hypersensitivity reaction rates [45]. A rapid antibiotic desensitization protocol has been developed and successfully used in 15 patients with CF, receiving 52 antibiotic desensitizations with only two severe hypersensitivity reactions; all patients completed desensitization [45]. Reactions during desensitization procedures are generally less severe than the initial hypersensitivity reaction, and no deaths have been reported in the last 10 years due to a reaction during a desensitization procedure [82,92]. For drug desensitization, pre-treatment with systemic glucocorticosteroids is not advised unless the patient has an underlying illness that requires such treatment [82].

Snake antivenom

In some regions of the world, venomous snake bites account for substantial morbidity and mortality. The main treatment is antivenom, but in up to 40% of cases, this may cause anaphylaxis [93]. In an effort to prevent anaphylaxis, drugs such as epinephrine, antihistamine and hydrocortisone are often given before antivenom as a prophylactic treatment, although there is a lack of evidence regarding the efficacy and safety of such practice. A recent systematic review and meta-analysis of seven trials of prophylactic medications in antivenom treatment found that pre-treatment with epinephrine was associated with substantial benefit. Treatment with glucocorticosteroids, whether alone or in combination with antihistamines, had no major benefits [94].

In a randomized double-blind controlled trial in Sri Lanka, de Silva *et al.* tested whether low-dose adrenaline (250 µg given subcutaneously), promethazine (25 mg intravenously) and/or hydrocortisone (200 mg intravenously), could prevent acute adverse reactions to antivenom. They found that, compared with placebo, pre-treatment with adrenaline reduced severe reactions to the antivenom by 43% at 1 h (odds ratio (OR): 0.57; 95% CI: 0.43–0.75; $p < 0.001$) and by 38% over 48 h (OR: 0.62; 95% CI: 0.51–0.74; $p < 0.001$). Neither hydrocortisone nor promethazine given alone reduced the rate of adverse reactions to the antivenom, and adding hydrocortisone negated the beneficial effect of adrenaline (OR: 1.50; 95% CI: 1.09–2.07; $p = 0.013$) [93].

Crotalidae Polyvalent Immune FAB–Ovine (CroFab) is an antivenom used predominantly for rattlesnake bites and the only US FDA-approved antivenom used in the USA. Reports suggest it is well tolerated in children and adults [95,96] and a recent systematic review and meta-analysis of 11 studies identified the incidence of immediate hypersensitivity reactions as 0.08% (95% CI: 0.05–0.11), although the incidence of anaphylaxis specifically is not recorded [97]. This indicates that CroFab is relatively safe compared with other antivenoms.

Other approaches to reducing risk & preventing anaphylaxis in healthcare settings

Reviewing the literature suggests a lack of effective, evidence-based strategies to prevent anaphylaxis in healthcare settings. As discussed, guidelines and treatment protocols are in place for treating patients with the most commonly implicated allergens, such as latex. However, a number of patient management factors may contribute to preventing a recurrence in patients with a previous history of anaphylaxis.

Detailed allergy history covering drugs, foods, other triggers

History taking, risk assessment and documenting allergies, especially to drugs, latex and food, is critical. Occupational history may indicate relevant risk, for example, exposure to latex. Clear and unequivocal documentation is essential: careful clinical history should be taken, records flagged, the patient should be given an allergy bracelet and anaphylaxis risk should be noted at the head of the patient's bed [4,12,31]. Patients are generally good informants about known allergies and should always be asked about these. However, patient reports of allergies are not a substitute for checking medical records, as patients may not understand information they have been given, may forget or may be confused, anxious or cognitively impaired. Therefore, both asking the patient about known allergies and checking records are recommended.

Information transmission

Information technology may help to prevent the risk of recurrent exposure in patients with known drug allergies by ensuring that the correct medication is administered at the correct dose at the correct time to the correct patient [98]. Strategies for providing real-time

clinical decision support and enhancing patient recognition are becoming more widely used in healthcare settings. These include: bar-coded patient wristbands allowing clinicians to access detailed, patient-specific drug allergy history; radiofrequency identification (RFID) technology, allowing access to patient records by scanning their wristband; biometric technology, such as fingerprint and iris scanning; patient-managed electronic health records; computerized warnings during transcription and administration of high-risk drugs and computerized decision support systems [99–102]. Where anaphylaxis occurs in one part of the healthcare system, such as the perioperative setting, ward staff, staff in recovery and staff who will care for the patient post-discharge from hospital need to be informed and records should be flagged to enhance patient safety.

Patient education

A recent Australian study, where researchers observed pre-anesthetic consultations between medical staff and patients, found that the terms 'allergy' and 'anaphylaxis' were poorly understood by patients, indicating the need to ensure that patients understand what information they are being asked to provide about their allergy history and the information they are given [103].

Lieberman *et al.* describe patient education as possibly the most effective anaphylaxis prevention strategy [4]. With any iatrogenically induced anaphylaxis, the implications of the diagnosis for future healthcare should be explained to the patient. A letter confirming the diagnosis, trigger if known and outlining a plan for future treatment should be sent to the patient and their general practitioner [19,57]. Patients need clear, personalized information on confirmed and suspected allergens, potential risks, the need to inform staff of allergies during further hospital admissions or attendances and the importance of using medical alert jewelry or carrying an allergy card or similar. Verbal information should be reinforced with written information, including a written summary of the anaphylactic event which they should be advised to bring to further healthcare consultations and hospital admissions. Information about reliable sources of information and how to contact support organizations will enable patients and their families to learn more about their allergy and how to manage risk [12,31,89].

Staff education

Healthcare staff, particularly those working in settings where there is enhanced risk of anaphylaxis, need to be trained on the implications of allergies in healthcare settings, with regular in-service updates and specifically trained in prevention, recognition and management of anaphylaxis. High-risk settings may benefit from a dedicated clinical lead to address patient safety concerns.

Importance of learning from system failures & improving outcomes

The increasing recognition of the risks associated with healthcare delivery has helped catalyze considerable global interest into how the risk of iatrogenic harm can be minimized. Key insights from this now substantial body of work include a

Box 4. Examples of reporting systems for anaphylaxis.**UK**

Medicines and Healthcare Products Regulatory Agency (MHRA) adverse drug reactions – the yellow card scheme <https://yellow-card.mhra.gov.uk/>

National Anaesthetic Anaphylaxis Database – reporting forms are available on the Association of Anaesthetists of Great Britain and Ireland (AAGBI) website <http://www.aagbi.org/safety/allergies-and-anaphylaxis>

National Reporting and Learning System (NRLS) for the National Health Service (NHS) National Patient Safety Agency (NPSA) in England and Wales <http://www.nrls.npsa.nhs.uk/patient-safety-data>

British Paediatric Surveillance Unit (BPSU), Royal College of Paediatrics and Child Health (RCPC)/Public Health England/Institute of Child Health initiative <http://www.rcpch.ac.uk/bpsu>

USA

MedWatch, the US Food and Drug Administration (FDA) Safety Information and Adverse Event Reporting Program <http://www.fda.gov/Safety/MedWatch/default.htm>

Patient Safety Reporting System (PSRS), associated with National Aeronautics and Space Administration (NASA) <http://www.psr.sarc.nasa.gov/programoverview/index.html>

Vaccine Adverse Event Reporting System (VAERS), sponsored by the US Department of Health and Human Services (HHS) www.vaers.hhs.gov

realization that much of this harm is due to systems failures, hence the need to understand how care processes can be strengthened to reduce the risks of similar events recurring. Key tools used by patient safety experts include root cause analysis and error reporting systems.

Local root cause analysis

This is a systematic means of investigating patient safety incidents, identifying service delivery problems and generating solutions, with the aim of preventing similar incidents occurring again through understanding the causes and actions needed for resolution [104]. This should, for example, be triggered if a patient with a known drug allergy received the drug to which they are known to be allergic, irrespective of whether this results in patient harm. The focus would be on identifying what went wrong, what could have been done better and what steps can be taken to prevent such events happening in the future.

Sharing events in local/national repositories

There is a notable lack of reliable information concerning the extent of patient safety incidents which contribute to anaphylaxis in healthcare settings. Reports to the National Reporting and Learning System for the NHS in England and Wales (NRLS) (unpublished data) indicate that the most frequent incidents resulting in potentially preventable anaphylaxis in UK healthcare settings involve patients being given drugs or

exposed to other substances to which they were known to be (and were documented as being) allergic, typically antibiotics, local/general anesthetics, analgesics, latex and contrast media. Examples of reporting systems are listed in Box 4; further examples can be found in Benn *et al.* [105].

Conclusions

Anaphylaxis is a rare, but potentially catastrophic event in healthcare settings. This review has highlighted that all patients are potentially at risk, hence the need for clinical staff being trained in the management of this allergic emergency and health systems having appropriate protocols and procedures in place to minimize risk. We have also sought to identify the patient groups and care contexts associated with increased risk and, as far as is possible given the limited evidence base, approaches that can be taken to minimize the risk of reactions developing and improving outcomes if a reaction occurs. From a clinical perspective, balancing the need for investigation and treatment of severe disease with risk of patient harm can be a challenge. Identification of patients at risk is a crucial aspect of prevention. Most prophylactic regimens are based on clinical experience rather than on objective evidence of their value.

Expert commentary

Epidemiological evidence has helped shed light on the risk of anaphylaxis in the population at large and the healthcare contexts and settings that increase the risk of anaphylaxis. It has however proved much more challenging to generate evidence to formally test interventions designed to prevent anaphylaxis, this, at least in part, reflecting the relative infrequency of reactions. That said, this review has identified a number of strategies that may be employed to reduce risk, both in the context of investigative procedures and the administration of interventions. A key overriding finding is given that any patient may unexpectedly develop anaphylaxis; it is therefore important that there are systems in place both to mitigate the risk of developing anaphylaxis, and for the early identification and appropriate

Table 1. Classes of narcotic drugs.

Naturally occurring	Semi-synthetic	Synthetic
Morphine	Diamorphine	Methadone
Codeine	Hydrocodone	Propoxyphene
Thebaine	Hydromorphone	Meperidine
	Oxycodone	Fentanyl

management of any reactions that actually develop. It is also important that health systems are optimally poised to learn from any systems failings to minimize the risk of iatrogenic harm.

Five-year view

Preventive medicine is in general a relatively underdeveloped field and, as demonstrated by this review, this is particularly true in the context of the primary prevention of anaphylaxis. Progress in identifying effective preventive interventions is likely to remain slow because of the relatively small numbers of individuals affected, which makes anaphylaxis a relatively uncompetitive field of enquiry when compared with, for example, the prevention of asthma and diabetes. The lack of commercial interest from the pharmaceutical industry is another important barrier to developing the evidence base for the prevention of anaphylaxis. Greater progress is anticipated in relation to the improved self and professional management of those with a prior history of anaphylaxis, which should, it is hoped, lead to a reduced risk of recurrent reactions.

Future developments for desensitization are likely to include safer, more standardized protocols; engineered recombinant proteins; CpG-oligonucleotide conjugated allergens, peptides or polymers of major allergens and a mixture of major recombinant allergens. Immunomodulators like omalizumab or anti-CD63 antibodies may be used for these desensitization protocols, particularly if the patient is at risk from multiple allergens [106–108].

There is also likely to be progress in the stratified medicines agenda through the identification of biomarkers that can better help to identify those who are likely to respond to treatments and also those who are most/least likely to experience adverse effects. This is a particularly important challenge in the context of expensive biological agents such as omalizumab. Antibody-based drugs have been clinically tested, including anti-IL-5,

anti-IL-4, anti-IL-13, anti-TNF- α , anti-CCR3, anti-CCR4 and anti-OX40L, with mixed results, but these offer promising therapeutic option for severe, poorly controlled asthma in the future, if biomarkers can be identified and characterized, allowing the selection of appropriate populations for clinical trials [109].

With the progressive move to electronic health record systems and associated decision support systems, it is also likely that there will be better real-time support to frontline clinicians on assessing risks and alternatives that can be used to minimize such risks.

Finally, given the welcome recent development of guidelines for the emergency and long-term management of anaphylaxis in recent years, consideration should be given to the development of a formal evidence-based guideline developed on the prevention of anaphylaxis in health settings. This should ideally be accompanied by a range of tools to support implementation and assess progress against agreed standards of care.

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Key issues

- Anaphylaxis is a medical emergency that may result in death.
- Although the majority of reactions occur in community settings, many healthcare procedures can trigger episodes of anaphylaxis.
- All health professionals should be trained in anaphylaxis recognition and management.
- In terms of patient populations, increased risk is established in those who have experienced previous anaphylaxis and allergic reactions and/or have evidence of allergic sensitization to foods, latex, radiocontrast media and drugs.
- Most reactions in healthcare environments will occur in the context of administration of treatments—in particular, antibiotics, immunotherapy/desensitization, anesthetics and analgesics, snake and antivenom and biological agents—and investigative procedures that involve allergen testing/challenge, radiocontrast media and latex-based equipment.
- There is at present very limited robust evidence on which to base decisions on anaphylaxis prevention.
- That said, this review has highlighted a number of steps that can be taken to try and minimize risk in the context of a range of relevant diagnostic and treatment procedures which, if implemented, should help to reduce the risk of anaphylaxis.
- Despite these measures, reactions will still on occasion occur; we have therefore also drawn on insights from patient safety science to draw attention to the importance of learning from systems failures and ensuring that any insights gleaned are used as a basis for enhancing the safety of health systems.
- This is an area where there is a need for considerable research and, given the major challenges in undertaking prevention studies, it is important this work proceeds in a collaborative manner if progress is to be made.

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