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ESSENTIALS Allergy is common and becoming commoner: it now affects about one-third of the UK population. This is being driven by environ- mental changes, which are also leading to an increase in both the complexity and severity of the condition. In addition to the trad- itional allergic disorders—asthma, rhinitis, and eczema—multisystem allergic disease and reactivity to several allergens are now common; new allergies have appeared, including those due to foods, drugs, and diagnostic agents; and anaphylaxis is increasing. In contrast, new cases of latex allergy have become uncommon. Where possible, patients with significant allergy should be re- ferred to an allergy specialist who can provide expertise not offered by—and complementary to—that of other specialties. Identifying and managing allergic causes of disease leads to reduction or resolution of its manifestations. Aetiology and pathogenesis Mechanism—allergy in its classical form occurs following inter- action of allergen with specific IgE antibody bound to high-affinity IgE receptors on mast cells, which results in mast cell activation, degranulation, and mediator release, but the same clinical pres- entation can occur as a result of IgE independent mast cell de- granulation (e.g. idiopathic anaphylaxis or angioedema). A normal subject has no specific IgE to common allergens and a low or normal total serum IgE level: production of specific IgE antibody requires a change in immunoregulation leading to sensitization (atopic state), with some sensitized subjects progressing to de- velop clinical allergy. Allergens—common allergic triggers include (1) inhaled allergens—house dust mite, pollens, and animal danders are the commonest causes of allergic asthma, rhinitis and eczema; (2) foods—commonly egg, milk, peanuts, and tree nuts; mainly cause acute reactions of varying severity (e.g. urticaria, angioedema, or anaphylaxis); (3) drugs—particularly antibiotics, aspirin, nonsteroidal anti-inflammatory drugs, and drugs given during general anaes- thesia, although allergy to other drugs/agents including insulin, radiocontrast media, and chlorhexidine is being described; (4) bee and wasp stings; (5) latex rubber—now less common. Clinical features and diagnosis Clinical presentation—this can be in various guises acute or chronic, with common manifestations being (1) allergic rhinitis—timing of symptoms indicates the causative allergen; (2) nonallergic rhinitis— some have aspirin sensitivity, rhinosinusitis, nasal polyps, and asthma; (3) conjunctivitis; (4) asthma—timing or circumstances of symptoms and exacerbations gives clues to aetiology; (5) eczema; (6) urticaria and angioedema—severe tongue swelling is a medical emergency and most often drug induced (especially angiotensin-converting en- zyme inhibitors) or idiopathic (non-IgE mediated); (7) anaphylaxis— presents with acute dyspnoea or hypotension/collapse, usually with cutaneous features such as erythema or urticaria. History taking—a good history is the key to diagnosis: too often the underlying allergic trigger is not identified and disease which could be ameliorated by allergen avoidance continues unchecked; aware- ness of drug and latex allergy are essential. In some conditions exclu- sion of allergy is

important. Clinical investigation—(1) serum tryptase—may be transiently ele- vated for up to 4 h following an acute reaction, but peaks at 1–2 h; (2) skin prick tests or serum-specific IgE assays—many patients have positive tests without symptoms, hence performing them in the ab- sence of appropriate clinical information is a common source of error; (3) intradermal and challenge tests—performed by allergy spe- cialists, mainly for diagnosis of drug and food allergy. Prevention and treatment Prevention—there are no widely applicable proven methods for pri- mary prevention of allergy. Emerging data suggests that early intro- duction of foods (e.g. peanut), in infants may prevent food allergy, particularly in those at high risk of allergy. Acute or chronic disease—management requires (1) allergen avoid- ance; and may also involve (2) pharmacotherapy—including non sedative antihistamines and topical corticosteroids (nasal sprays, inhalers, and creams); and, less commonly, (3) immunotherapy (de- sensitization)—should be offered to patients with poorly controlled allergic rhinitis or venom anaphylaxis. Anti-IgE therapy should be considered for severe asthma or urticaria refractory to standard therapy. Other monoclonal antibodies are being introduced. 4.5 Allergy Pamela Ewan

4.5 Allergy 369 Anaphylaxis—first-line treatment is intramuscular adrenaline (epi- nephrine). All patients should subsequently be referred to an allergy specialist for diagnosis and management: allergen or trigger avoid- ance (e.g. food or drug), reduces further episodes and should be combined with an adrenaline autoinjector for early self-treatment. Introduction Allergic disorders are wide ranging, and include asthma, eczema, rhinitis, anaphylaxis, angioedema, and urticaria. Some disorders will always be allergy driven (e.g. food, venom, or latex allergy), whereas others (e.g. asthma or rhinitis) may be allergic or non- allergic, but the role of allergy is increasing. Allergy has increased in prevalence, severity, and complexity over the last four decades, with a resulting burden on patients and cost to health services. Failure to make an allergy diagnosis adversely affects manage- ment and outcome. Avoiding a food or a drug can completely ameliorate disease, yet many allergic disorders are treated with pharmacotherapy only. Allergy practice involves both IgE-mediated (classical allergy) and non-IgE-mediated disorders. In the latter group—which in- cludes certain types of anaphylaxis, angioedema, and rhinitis—the signs and symptoms mimic IgE-mediated allergy because release of mast cell mediator occurs, but IgE is not involved. Historical perspective Early descriptions of allergy exist. Hay fever was described in 1873 by Charles Blackley, who demonstrated that pollen was the cause by applying pollen grains to his nose and eye in winter and reproducing the symptoms. Passive transfer of sensitivity to the skin by injecting serum from a fish allergic person to a nonallergic subject was dem- onstrated by Prausnitz and Kustner in 1921 but it was not until 1967 that the serum factor (reagin) was shown to be a new class of im- munoglobulin, IgE, by the Ishizakas in the United States of America and then by Bennich and Johansson in Sweden in 1971. Aetiology and pathogenesis Type I hypersensitivity (allergic) reactions The term ‘allergy’ is used variably. It is often used synonymously with the type I IgE-mediated reaction described by Gell and Coombs. Interaction of allergen with specific IgE antibody bound to high- affinity IgE receptors (FcεRI) on mast cells results in mast cell acti- vation, degranulation, and mediator release (Fig. 4.5.1). Histamine and other mediators including leukotrienes and prostaglandins cause vasodilation, smooth muscle contraction, mucosal oedema, and secretions. Non-IgE-mediated reactions Mast cell activation and mediator release may occur independent of IgE antibody. Certain drugs and physical stimuli (e.g. pressure on the skin, cold, or exercise) do this in susceptible individuals. However, it can also occur without a recognized trigger. Mechanisms are poorly understood. Steps in the development of allergy A normal subject has no specific IgE to common allergens and a low or normal total serum IgE level—the nonatopic state.

Production of specific IgE antibody requires a change in immunoregulation with a switch from the Th0/Th1 state to a Th2 dominant state. This may result from failure of function of T regulatory cells, which produce interleukin-10 (IL-10) and transforming growth factor β. Th2 cells secrete the cytokines IL-4 and IL-13 which result in B cell switching to IgE production (atopic; Fig. 4.5.2). The atopic state often has no associated symptoms: this is known as sensitization. A proportion of sensitized subjects progress to develop clinical al- lergy (allergic). Prevalence Atopy Atopy is defined as the presence of specific IgE to one or more common allergens. Specific IgE can be detected by skin prick testing. The incidence of atopy in the general population is high, many studies previously showing rates of about 40%, but this appears to be rising. In a study in the United States of America, the third National Health and Nutrition Examination Surveys conducted between 1988 and 1994, 54% of the population tested had positive skin prick tests to 1 or more of 10 common allergens (i.e. they were atopic). This was an increase compared to the findings in an earlier study (1970 to 1980), with prevalences two to five times higher for the six allergens common to both studies. Mast cell Allergen Specific IgE Mediator release Histamine Fig. 4.5.1 The type I allergic reaction. Reproduced from the BMJ, Pamela W. Ewan, 316(7142):1442–5, © 1998, with permission from BMJ Publishing Group Ltd. Nonatopic Atopic or sensitized Clinical allergy Specific IgE positive Symptomatic Specific IgE positive Asymptomatic Specific IgE negative Asymptomatic Fig. 4.5.2 Stages to the development of allergy.

370 SECTION 4 Immunological mechanisms Sensitization as a predictor of allergy Various studies suggest that sensitization is a predictor of later al- lergy. In some infants, sensitization to egg precedes and predicts the development of eczema and/or peanut allergy. Early sensitization to food allergens in the first year of life is also a predictor of subsequent sensitization to inhalant allergens, which in turn predicts the inci- dence of asthma and hay fever in young adulthood. Clinical allergy It is not possible to provide precise prevalence data for allergy overall. There are incomplete or missing data for some allergic dis- orders (e.g. drug allergy and anaphylaxis); allergy is involved in a subset of certain diseases (e.g. eczema or asthma); and different manifestations of allergy occur in one individual (multisystem al- lergic disease). A picture can be built up, however, with minimum estimates for number of people affected. In the United Kingdom, about 18 million (39% of children and 30% of adults) have been diagnosed with one or more of asthma, eczema, and rhinitis. A considerable proportion of this is allergic in origin (e.g. 26% of the population has allergic rhinitis). Serial surveys show that the prevalence of asthma, rhinitis, and ec- zema has increased about threefold over three decades, and this is thought to be due to an increase in the prevalence of allergy. Comorbidity is common and increases the likelihood of allergy being involved. Food allergy occurs in about 3% of adults and 4% of children— 1.8 million people in the United Kingdom. Nut allergy, where there are more accurate data, occurs in 1–2% of children in de- veloped countries and a growing number of adults as this allergy emerged in the mid-1990s in more than 460 000 individuals in the United Kingdom. Venom allergy occurs in about 2% of the population. There are incomplete epidemiological data on anaphylaxis. The lifetime risk of symptoms suggestive of anaphylaxis in the general population as reported in surveys of the public, is at least 1.6%. Results of several studies in Europe suggest an incidence of 1.5–7.9 per 100 000 person-years and a prevalence estimated at 1 in 300. United Kingdom data shows that the number of hospital admissions for anaphylaxis rose by 615% from 1992 to 2012 (Fig. 4.5.3). The same picture is seen in developed countries worldwide. The absolute numbers do not reflect prevalence as only a minority is admitted, most being managed in emergency departments, however the trend is clear. Admission rates and fatalities from drug and venom al- lergy predominate in older people.

Food-induced anaphylaxis is commonest in children and fatal food reactions in the teens and early twenties. Taking individual causes, food, and venom allergy cause anaphylaxis in a few million people in the United Kingdom. Since 1990, hospital admissions for food allergy, urticaria, and angioedema have also increased. Important areas where there are few data are drug allergy and angioedema. Even for penicillin allergy, where there are most data, prevalence data is incomplete. About 5.9 million people in the United Kingdom are labelled as penicillin-allergic, yet only about of 10% of these are truly allergic. There are no data on prevalence of sensitivity to aspirin, NSAIDs, or other analgesics—an increasing problem. There are several new allergies (e.g. to fruits and vegetables and sesame), where information is incomplete. Complex or multisystem allergic disease is now common. Allergic asthma, rhinitis, and ec- zema commonly coexist, and food allergies occur mainly in patients with these disorders. Latex allergy is now uncommon, following the introduction of nonpowdered latex gloves. Aetiology: Allergens The allergic trigger varies with the disorder and to some extent with the age of the patient. • Inhaled allergens are the commonest cause of allergic asthma, rhin- itis, and eczema, especially house dust mite, pollens, and animal danders. These three allergens are the most common causes of al- lergy in the United Kingdom. Alternaria and Cladosporium are important causes of acute seasonal severe asthma (and/or rhinitis) in late summer. Eczema in adults or older children may be driven by house dust mite allergy. 10 8 6 4 2 0 1995 2000 2005 2010 Male lCD change 4-hr wait target introduced Female Year Hospital admissions for anaphylaxis per 100 000 population 0.10 0.05 0.00 Male Female 1995 2000 2005 2010 Year Fatalities due to anaphylaxis per 100 000 population (a) (b) Fig. 4.5.3 Rising hospital admissions for anaphylaxis. Reproduced from Turner PJ, et al. (2015). Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992–2012. J Allergy Clin Immunol, 135, 956–63.e1.

4.5 Allergy 371 • Foods commonly responsible for allergy include egg, milk, peanuts, and tree nuts. Others are fish, shellfish, fruits, vegetables, sesame, seeds, and soya. These will mainly cause acute reactions of varying severity (e.g. urticaria, angioedema, or anaphylaxis). In toddlers, foods, particularly egg or cow’s milk, are important triggers for eczema. • The important drugs are antibiotics, aspirin, nonsteroidal anti- inflammatory drugs (NSAIDs) and drugs given during gen- eral anaesthesia, especially the neuromuscular blocking agents. Insulin, opiates, and vaccines are rarer causes of systemic allergic reactions. Local anaesthetic rarely causes allergy, although it is commonly perceived. Diagnostic dyes, chlorhexidine, intra- venous colloid, and radio contrast media occasionally cause anaphylaxis. • Bee and wasp venoms cause systemic allergic reactions of varying severity including anaphylaxis. • Latex rubber causes a variety of symptoms including urticaria, angioedema, asthma, rhinitis, and anaphylaxis. Prevention Primary prevention Environmental factors play an important role in the development of allergy. The hygiene hypothesis suggests that early exposure to microbial infection is protective, driving Th1 responses (e.g. chil- dren exposed to endotoxin from farm animals were less likely to develop allergic disease). Avoiding exposure to food allergens in early life (maternal diet during pregnancy and lactation and the infant’s diet), was sug- gested in 1998 as a means of preventing allergy, but the effect is not established. The lack of evidence was confirmed in a gov- ernment committee review in 2016. Emerging data suggests the opposite, that early introduction of foods (peanut and egg), par- ticularly in higher-risk infants may induce tolerance and prevent food allergy.
Secondary prevention Treatment with oral antihistamine has been shown to prevent or delay the development of asthma in infants with atopic dermatitis sensitized to grass pollen or house dust mite. Immunotherapy for rhinitis can prevent the development of asthma. Clinical features The

history is the key to reaching an allergy diagnosis (Box 4.5.1). This is supported by appropriate tests, particularly those for specific IgE. Knowledge of allergens, their seasons, sources, and disorders they may cause, as well as presentations and patterns of disease, is essential. Enquiry should be made into the timing of symptoms and the effect of allergen exposure (there may be multiple manifestations of allergy). Some of the 'allergic' diseases, including asthma, rhinitis, eczema, and anaphylaxis, may be IgE-mediated or non-IgE-mediated. This distinction needs to be drawn. In the allergic group, the allergic cause should be identified. The likelihood of allergy is increased • in children and young adults; • if multiple systems are involved (e.g. asthma, rhinitis, eczema, food allergy). Allergic rhinitis Symptoms include rhinorrhoea, nasal congestion or obstruction, and sneezing. The dominant symptom varies with the allergen. Pollen allergy (hay fever or seasonal allergic rhino-conjunctivitis) mainly causes sneezing, nasal itch, and profuse watery secretions as well as itchy watering eyes. The timing of the symptoms indicates the causative allergen (e.g. tree pollen allergy occurs in spring, grass pollen in early summer, and late summer and autumn symptoms are due to shrub or weed pollens or the moulds Alternaria and Cladosporium). In perennial allergic rhinitis, nasal congestion and secretions are the main features. There may be a history of triggers responsible for exacerbations, as well as remissions when away from the allergen. House dust mite allergic patients are often worse on waking (fol- lowing exposure from mattress and bedding overnight), or after cleaning, and better at altitude (dust mite does not survive above 1000 m). Animal allergy is usually evident from exacerbations on contact, or remissions away from home if a pet is kept there. Highly allergic subjects react to exposure to small amounts of hair on the clothing of others, without direct animal exposure. In horse allergy, a few hairs can cause severe periorbital oedema or asthma. Nonallergic rhinitis In non-IgE-mediated rhinitis, symptoms are perennial but intermit- tent and variable. A subgroup has aspirin sensitivity, rhinosinusitis, nasal polyps, and asthma. This is often severe, with marked nasal obstruction, and difficult to control. Conjunctivitis This mainly occurs in association with rhinitis, especially due to pollen but also to animals and dust mites. In a small number of patients with hay fever, isolated conjunctivitis and periorbital oedema occurs. Severe disease can result in conjunctival oedema and impaired vision. Asthma Allergy plays an important role in most asthma in children and young adults. The importance of identifying the allergic trigger is that avoid- ance can significantly modify disease and reduce drug consump- tion. The timing and circumstances of symptoms and exacerbations Box 4.5.1 Key knowledge and actions for the physician • Awareness of disorders where allergic aetiology should be considered • Management of allergic medical emergencies—anaphylaxis (IM adren- aline first line)—tongue or laryngeal oedema • Measure acute serum tryptase in suspected anaphylaxis • After suspected anaphylaxis provide adrenaline autoinjector • Avoiding the triggering agent in drug, food, or latex allergy • Interpretation of specific IgE results to avoid diagnostic error (positives often indicate sensitization and not clinical allergy) • Document and check for drug allergy; distinguish drug allergy from intolerance • Have established referral route to allergy

 Immunological mechanisms gives clues to aetiology. In pollen asthma, symptoms are seasonal. Alternaria allergy results in acute severe attacks of asthma at har- vest time (July and August in the United Kingdom), when allergen is released resulting in sudden peak levels. Many patients have had hospital admissions with asthma at that time of the year. Accurate allergy diagnosis means that prevention measures can be put in place. Other causes are animals: exposure to cat, dog, or horse may induce acute wheeze. In a subset this can be life-threatening. House dust mite allergy is a major cause of perennial asthma. Eczema Atopic eczema

in children most commonly affects the flexures and neck. In severe cases it may be widespread. It is more difficult in eczema to identify triggers from the history. Sometimes exacerbations are obvious (e.g. after contact with animals or if both eczema and rhinitis are exacerbated by dust exposure). House dust mite allergy is an important trigger. Scratching at night will rub allergen into the skin, driving the disease. Food allergy causes eczema in children. A problem is that many patients with eczema have specific IgE antibody to multiple allergens, many of which are not clinically relevant. If there is no clear history of flares with allergens, interpretation of allergy tests can be difficult. A trial of allergen exclusion over a few weeks is then required for diagnosis. Urticaria and angioedema These may occur separately or together. Urticaria is common. Acute episodes may be allergic (see earlier) but chronic urticaria, defined as daily symptoms lasting for 6 weeks, is rarely allergic. Urticaria con- sists of itchy wheals, raised lesions with pale centres and surrounding erythema. Wheals are of varied size and usually occur in crops on the limbs or trunk but can be extensive. Lesions tend to be short lived, but as one crop fades another appears. In giant urticaria, lesions the size of the palm of the hand occur. These are more oedematous and take longer to resolve. When urticaria and angioedema coexist, urticaria is usually dominant with occasional episodes of angioedema. It is important in chronic urticaria to determine aetiology. The usual assumption is that this is allergic, and foods are often impli- cated, leading to restricted diets, but most urticaria is non-IgE medi- ated (idiopathic). Ruling out allergy is important. Some is related to auto-immunity. Some is physical, triggered by heat, cold, exercise, pressure on the skin, or contact with water. In cold urticaria, chilling of the skin (e.g. by putting the hands in cool water or exposure to cold wind) causes erythema and pruritus. After more prolonged exposure, angioedema occurs. If a large surface area is involved, as in sea swim- ming, hypotension and loss of consciousness occur. Drugs, especially NSAIDs and aspirin, are an important cause of acute attacks. Infection commonly triggers urticaria, especially in children. Angioedema The commonest sites for angioedema are the lips and eyelids. This type of angioedema often occurs with urticaria but may occur alone. Angioedema may also involve the tongue and larynx, pharynx, or uvula. Swelling is often unilateral. Tongue swelling usually occurs alone, without swelling at other sites or urticaria. Angioedema of the whole tongue can cause respiratory obstruction, cyanosis, or respiratory arrest. Severe tongue swelling is a medical emergency. Tongue swelling is mostly drug induced (especially angiotensin converting enzyme inhibitors) or idiopathic (non-IgE mediated). If the patient is taking an angiotensin-converting enzyme inhibitor, the first step should be to stop the drug. Angiotensin converting enzyme inhibitor induced angioedema is thought to be due to activation of the kallikrein-kinin system with bradykinin generation. The diagnosis is made from the history combined with exclusion of other causes. There is no confirmatory laboratory test. Onset is either within weeks of starting medication or, confus- ingly, after an interval of many months or years. It is a class effect. Angiotensin II receptor antagonists are usually tolerated. Most iso- lated angioedema is nonallergic. There is no erythema or pruritus. Allergic (IgE-mediated) angioedema When angioedema is allergic, other features are usually present. Horse, other animal and pollen allergy cause periorbital oedema but usually with conjunctivitis and/or conjunctival oedema; there may also be rhinitis and asthma. Food allergy commonly causes perioral angioedema but there will also be perioral urticaria and oral prur- itus and systemic features, such as abdominal pain or vomiting, may occur. In latex allergy the angioedema will be periorbital or perioral if there has been local rubber contact (e.g. rubber goggles, swim- ming cap, or blowing up a balloon). Pruritus, erythema, and urti- caria will be present. Hereditary angioedema (HAE) and C1 inhibitor deficiency C1 esterase inhibitor deficiency is a rare autosomal dominant dis- order (hereditary angioedema, HAE) but may sometimes be acquired (acquired angioedema, AAE). HAE is a distinct disorder, due

to the deficiency or dysfunction of the complement protein C1 inhibitor. In acquired angioedema, there is depletion of C1 inhibitor due to com- plement activation by monoclonal or auto-antibodies. C1 inhibitor is a key regulator of the Factor XII/kallikrein proteolytic cascade that leads to bradykinin production. The deficiency results in unopposed activation of the kallikrein system, leading to generation of brady- kinin, which causes increased vascular permeability and oedema. The deficiency also results in activation of the classical complement pathway, with generation of the peptides C3a and C5a, which cause increased capillary permeability and smooth muscle contraction. In type 1 HAE (which accounts for about 85% of patients), there is a low level of C1 inhibitor in serum (immunochemical assay low); whereas in type 2, there is a functional defect and the immunochemical assay for C1 inhibitor is normal, but the functional assay is extremely low. In HAE there is a usually a family history, but spontaneous mutations arise. These various forms have similar clinical features and man- agement. There is another form of HAE, extremely rare and difficult to confirm, having the clinical features of HAE often with a family history but no complement abnormalities (HAE with normal C1 in- hibitor), sometimes associated with mutations in the gene for factor XII. AAE mainly occurs in older patients, has no family history, and is associated with an underlying, usually lymphoproliferative, dis- ease. Treatment of the underlying condition results in a return to normal of the C1 inhibitor level. Angioedema affects the skin or mucosa and occurs at one or more of three sites: cutaneous, intestinal, and laryngeal. There is no ur- ticaria. Patients present with peripheral swellings, typically flitting, involving different sites in different attacks—hence distinct from idiopathic or allergic angioedema which is restricted in site, usually lips or eyelids. The hand, limbs, and genitals are often affected. If the face is involved the swelling is more extensive and not limited to lip or eye. Intestinal mucosal oedema, which causes partial intestinal

4.5 Allergy 373 obstruction, presents with abdominal pain and vomiting. The least common but most severe manifestation is laryngeal oedema, which is life-threatening and can be fatal. Attacks are self-limiting, lasting 48 to 72 h, and of variable severity. Although the angioedema re- solves spontaneously without treatment, laryngeal oedema can cause asphyxia and severe attacks the gastrointestinal tract mucosal oedema result in subacute intestinal obstruction. Attacks are inter- mittent, with many months between episodes when patients are well. The diagnosis of HAE should be suspected from the characteristic clinical picture which is distinct from other causes of angioedema. The different pattern and distribution of angioedema combined with attacks of unexplained abdominal pain, differentiate this from idiopathic angioedema. However, diagnostic delay of many years is usual, and these patients have commonly had repeated emer- gency attendances or admissions and sometimes laparotomies. Confirmatory investigations are low C4 and C1 inhibitor levels. Treatment should be managed by a specialist. Prophylactic treat- ment is with the attenuated androgen, danazol, which increases the hepatic production (by the normal gene) of C1 inhibitor. Only a mar- ginal increase in C1 inhibitor is required to control the disease and levels of C1 inhibitor remain profoundly low. There have been con- cerns about side effects of danazol, compounded by the use of unneces- sarily high doses. Low or moderate doses of danazol prevent attacks in many patients, thus limiting side effects. The approach should be to gain control then reduce the dose, titrating this down until a few mild breakthrough attacks occur. Some patients are controlled on as little as 100 mg twice weekly. Determining the minimum effective dose limits or avoids side effects. This is the first-line approach in most patients, but danazol cannot be used in prepubertal children or pregnancy. Tranexamic acid can be used in children but is much less effective than danazol. Fortunately, HAE may not present until the teens. There are

several treatments for acute attacks. This may be by replace- ment with intravenous C1 inhibitor concentrate derived from plasma. A newer recombinant C1 inhibitor concentrate is available but in trials, effectiveness was not established in patients with laryngeal attacks. Drugs that target the downstream pathways involved in C1 inhibitor deficiency are alternatives for acute attacks and include the bradykinin B2 receptor antagonist, icatibant and ecallantide, a recombinant plasma kallikrein inhibitor (not licensed in the United Kingdom), both for subcutaneous injection. All of these are high cost. Icatibant comes in a prefilled syringe suitable for self-injection and home use. There is a delay of a few hours to the onset of symptom reduction, so it is dangerous for patients with laryngeal attacks to remain at home and they must imme- diately attend the emergency department after self-injection. In some patients C1 inhibitor appears to be more effective than icatibant. There are encouraging efficacy results from trials of a new kallikrein inhibitor, lanadelumab which is now licensed. This is a recombinant fully human monoclonal antibody and the first therapeutic agent to allow sustained inhibition of kallikrein and limit bradykinin generation. Home therapy with icatibant or intravenous C1 inhibitor concen- trate is being used to give earlier control and avoid emergency de- partment visits. This approach may encourage some patients to stop danazol prophylaxis due to fears about side effects putting them at more risk of life-threatening reactions. Patients should have fast track arrangements with their local emergency department and, as this is a rare disease, carry an information sheet/treatment plan. A proposal is for prophylaxis with C1 inhibitor or icatibant (e.g. twice weekly) in patients having frequent attacks, but this occurs in very few patients. Anaphylaxis Anaphylaxis is an acute severe systemic reaction of rapid onset. There is no universally agreed definition. There are many features, not all of which need be present (Box 4.5.2). One of the two severe features, respiratory difficulty, or hypotension, should be present. Severe dyspnoea is due to laryngeal oedema, often described as a sensation of the throat closing up, or acute asthma. Hypotension presents as weakness, difficulty standing, collapse, or loss of con- sciousness. Cutaneous features are usually present. Rarely profound hypotension with loss of consciousness is the only feature, mostly after bee or wasp stings or intravenous drugs. The main causes of anaphylaxis are foods, drugs, and venom al- lergy or idiopathic reactions. Food accounts for around 90% of childhood anaphylaxis, whereas in adults, food, venom, and drug allergy and idiopathic reactions each account for approximately a quarter of cases. In food-induced anaphylaxis, respiratory symp- toms are the dominant severe feature. In contrast, in venom allergy or allergy to an intravenous drug, hypotension predominates. Thus, the clinical picture varies with the cause of the anaphylaxis. Non-IgE-mediated (idiopathic) anaphylaxis is becoming more common. This usually presents in a different way and with a slightly slower evolution. It often begins with pruritus of the palms and soles, then progresses to general pruritus, erythema, and urticaria, with diarrhoea, abdominal pain, and hypotension. Respiratory symp- toms are uncommon. Food allergy Different foods cause different patterns of disease: with differences in severity, clinical features, comorbidities, and likelihood of reso- lution or persistence. Severity varies from mild, usually facial and oral urticaria/oedema, to anaphylaxis (Table 4.5.1). Egg and cow’s milk are the commonest food allergies in infants and toddlers. Egg allergy Egg allergy is mostly mild or moderate. Symptoms include perioral or facial erythema, urticaria, and angioedema, often with vomiting. Diarrhoea is rare. In more severe egg allergy asthma and anaphylaxis occur. Egg allergy can be partial and at presentation the child may

Box 4.5.2 Clinical features of anaphylaxis • Erythema • Pruritus • Urticaria • Angioedema • Laryngeal oedema • Asthma • Nausea, vomiting, abdominal cramps • Sense of impending doom • Fainting, light-headedness • Collapse • Loss of consciousness • Fits (rare) • Incontinence (rare)

 tolerate a low allergen dose (e.g. egg as a baked ingredient, but not whole cooked egg). Most egg allergy in infants and young children resolves by or before school age. Management includes exclusion of egg from the diet and review to decide on timing and pace of gradual egg reintroduction. In the minority where disease persists, this can be severe, as can adult-or teenage-onset egg allergy. The measles, mumps, and rubella (MMR) vaccine does not contain egg protein and can safely be given. Inactivated (injected) influenza vaccines that are egg-free or contain egg protein, at very low levels, can be given to most patients with egg allergy. Children from age 2 years with egg allergy should be vaccinated with the nasal influenza vaccine. Yellow fever vaccine contains egg thus specialist advice is re- quired.
A desensitization protocol and incremental dose regime have been trialled and shown to be effective in a small number of patients. Cow's milk allergy Mild to moderate cow's milk allergy causes similar symptoms to egg al- lergy, but gastrointestinal symptoms with vomiting, abdominal cramps, and diarrhoea are more common. Most milk allergy in infancy resolves early. Where disease persists it can be severe, tiny quantities of milk protein causing anaphylaxis. Non IgE-mediated reactions against cow's milk are described as cow's milk protein intolerance. Clinical presen- tation overlaps with milk allergy, but gastrointestinal symptoms and eczema predominate. This usually resolves by the age of 12 months. Nut allergy Nut allergy has the propensity to cause severe life-threatening reactions. In the mid-1990s, when this disorder first appeared in significant num- bers, about two-thirds of cases were severe with airway involvement, either laryngeal oedema or asthma. Peanuts account for most food- induced fatal and near-fatal reactions. In these airway obstruction and asphyxia occur. The diagnosis of peanut allergy therefore causes anxiety. Although about two-thirds of individuals now have a history of mild disease there is the risk of reactions becoming more severe. Peanut is a legume, not a nut; it is thus botanically distinct from tree nuts—nonetheless, allergy to both in an individual is frequent. Peanut is the most common 'nut' to cause reactions. Of the tree nuts, Brazil nuts, almonds, hazelnuts and cashew nuts most frequently cause allergy. Brazil nuts and cashew nuts result in the highest pro- portion of severe reactions. Most peanut-allergic subjects are not al- lergic to pulses such as peas and beans. Nut allergy mostly begins in childhood. The average age of onset of peanut allergy is 2 years. Allergy to tree nuts then appears progres- sively during childhood, but some patients remain 'monoallergic'. Allergy presenting in older children or adults is more likely to be due to a tree nut. There is a strong association with atopy: 96% are atopic and about two-thirds have asthma, rhinitis, or eczema. Kiwi fruit allergy This is one of several newer food allergies. Kiwi allergy began to appear after the introduction of kiwi fruits to the United Kingdom food market, and the incidence gradually rose in parallel with con- sumption. The main symptoms are perioral urticaria and oral mu- cosal oedema, but anaphylaxis with laryngeal oedema may occur. Oral allergy syndrome This is new disorder, emerging over the last two decades and now very common. It is allergy to fruits and sometimes vegetables or nuts in patients with tree or grass pollen allergy (spring or summer hay fever). The primary sensitisation is to pollen and the major al- lergens in certain fruits show structural homology with the major birch pollen allergen. Stoned fruits (e.g. apple and peach) are the commonest cause. Symptoms are oral, palatal, and pharyngeal itch and mucosal oedema. The food is tolerated when well–cooked as the allergens are heat labile. This is thought to be a mild disorder, but over time a small subset with more marked symptoms has emerged. Severe allergy to fruit is increasingly recognized. This appears to be a distinct disorder where the IgE is directed against different allergen components to those in oral allergy syndrome. Similarly, primary nut allergy, potentially more severe, should be distinguished from oral al- lergy syndrome to a nut. The differential diagnosis can be supported by component resolved diagnosis, measuring the cross-

reacting subset of specific IgE (PR-10 proteins) found in OAS and the IgE to storage pro- teins found in primary allergy. For example, in peanut allergy, IgE to the PR-10 peanut protein, ara h8, is found in oral allergy syndrome whereas IgE to ara h2, the seed storage protein, is found in primary peanut allergy. Fish and shellfish These causes urticaria, angioedema, and vomiting. Severe anaphyl- actic reactions occur. Fish and shellfish allergy often occur separ- ately and within fish allergy, not all fish types may be involved. Hymenoptera venom allergy Bee or wasp (yellow jacket) stings are an important cause of anaphylaxis but cause allergic reactions of varied severity, from urticaria through to anaphylaxis. Hypotension is common in severe venom reactions. Wasp sting allergy is more common in the United Kingdom. Bee sting allergy mainly occurs in beekeepers and their relatives (i.e. those frequently stung). The pattern of reactions varies but need not be progressively worse. A factor favouring a less severe reaction subsequently is a long interval between stings. Rarely, these stings can be fatal. A risk factor for very severe reactions is a raised baseline tryptase, indicating suscepti- bility to mast cell activation. For further information see Chapter 10.4.2. Drug allergy Evidence from national patient safety incident reports and from re- search shows that a large number of NHS patients with known drug allergies are re-exposed to these drugs in error each year (of 18 000 preventable drug incidents, 80% were in patients with known allergy). Many people have been inaccurately diagnosed and recorded as ei- ther having or not having a drug allergy. While re-exposure to a drug Table 4.5.1 Varying presentations of acute allergic reactions to foods according to severity Severity Clinical features Mild Cutaneous features only: pruritus, erythema, urticaria, or mild angioedema Moderate The above, plus more severe angioedema and/or vomiting, abdominal pain, and/or mild dyspnoea or tightening of throat Severe The above, plus respiratory difficulty (laryngeal oedema or asthma) and/or hypotension (less common)

 has not caused harm in the majority of people, a minority of these incidents have caused harm or death. One of the commonest errors is administration of co-amoxiclav to a penicillin allergic patient. Better recognition and documentation of drug allergy is essential. Diagnosis can be difficult and many reactions are falsely labelled as drug allergy. Penicillin, muscle relaxants, insulin, and other hor- mones act via IgE-mediated mechanisms, whereas NSAIDs and acetyl-cholinesterase inhibitors, produce angioedema and ana- phylaxis or adverse reactions by non-IgE-mediated mechanisms. Opiates can cause IgE and non-Ige mediated reactions. However, this is a complex area and antibiotics including β lactams, may also cause reactions through other mechanisms (e.g. T-cell mediated as one possibility). IgE-mediated reactions to β-lactam antibiotics), re- sult in rash, angioedema, or anaphylaxis. Less severe reactions in- volve rash which may be maculopapular or urticarial, and mainly follow oral administration. Reactions usually occur after one dose or 1 to 2 days into treatment. Anaphylaxis occurs after parenteral ad- ministration (within minutes of intravenous administration) but is described, rarely, after oral treatment. Always check for drug allergy before administering an intravenous drug. With the increased use of antibiotics, more patients are developing allergy. Some patients are allergic to more than one class of antibiotic. Investigation is not simple and for the most part blood tests are not helpful. Serum IgE to penicillin has such poor predictive value (sen- sitivity 0–25%) it should not be used alone. Specialist allergy referral is required and investigations include skin prick tests, intradermal tests (with late reading if T-cell mediated reactions are suspected) and drug challenge. The latter is often required in penicillin allergy, as up to 30% of patients cannot be identified on skin testing alone. Most penicillin allergic patients tolerate aztreonam or carbapenems (e.g. all of a series of 212 patients) but rare cross reactivity between penicillins and these drugs has been reported.

Sensitivity to aspirin and NSAIDs presents with urticaria and angioedema or with asthma and laryngeal oedema. The time of onset in relation to drug admin- istration depends on the route and formulation: 30 to 60 min after oral nonenteric coated preparations and several hours after slow-release preparations. Intravenous or rectal administration results in more rapid onset, often 15 to 30 min. Anaphylaxis during anaesthesia may be due to the anaesthetic agent, usually a neuromuscular blocking agent. However, increasingly other drugs administered are responsible. These include antibiotics, NSAIDs, opiates, chlorhexidine, diagnostic agents, and colloid. If a drug reaction is suspected, it is important to document the de- scription, all drugs being taken at the time, and the time of onset in relation to duration of drug administration, as detailed in the NICE drug allergy guideline (Table 4.5.2). Latex allergy Latex allergy causes reactions of varying severity. Most are mild to moderate, with contact erythema, urticaria, and angioedema. This can remain localized or become generalized as the allergen is ab- sorbed. Most reactions occur in medical settings, from latex gloves or equipment. Thin, stretchy rubber products such as surgical gloves are most allergenic, whereas black solid rubber is inert and causes few reactions. Exposure through contact with dentists' gloves causes local symptoms in the mouth or face. Absorption from surgeons' gloves may occur through the peritoneum or mucosal surfaces (e.g. vaginal examinations during labour) resulting in anaphylaxis. In daily life exposure may be from condoms, household gloves, swimming caps, and so on. Blowing up balloons leads to perioral angioedema. Inquiry into the effect of these exposures can elicit whether a pa- tient has latex allergy. Almost all patients with latex allergy are atopic and have other allergies such as asthma, rhinitis, and eczema. There is a strong association with hand eczema, and broken skin increases Table 4.5.2 Approach to drug allergy (adapted from NICE guideline 2014) Assessment Document signs, time of onset, suspected drug, other drugs Immediate reactions (early onset c.1 h) may include: erythema, urticaria, angioedema, hypotension and/or bronchospasm Nonimmediate (onset after 3–6 days) reactions without systemic symptoms red macules or papules (exanthema-like) Nonimmediate reactions with systemic involvement (e.g. DRESS, Stevens–Johnson syndrome, toxic epidermal necrolysis) Acute investigation Measure serum tryptase Documentation and sharing information Document allergy/suspected allergy in medical records Complete allergy box Share drug allergy status With patient, in GP letters, discharge summaries Patient wrist bands Distinguish drug allergy from adverse drug reactions Check drug allergy status before prescribing or administering any drug Nonspecialist management Stop drug Treat reaction Document Refer to specialist (if indicated) Allergy specialist Provide written advice on: Drug allergy Investigations used to confirm diagnosis; which drugs to avoid, and drugs safe for future use

376 SECTION 4 Immunological mechanisms absorption of latex. About 50% have food allergy due to cross-reacting allergens. This association was originally made for banana, avocado, and melon, but a wide variety of foods may be involved. A latex al- lergic subject need only avoid foods to which allergy has been proved. However latex allergy has become uncommon since the intro- duction of nonpowdered latex gloves. Nonlatex gloves (e.g. nitrile) are also used for many healthcare tasks. In the past, latex allergic subjects were often healthcare workers—medical, nursing, dental, and ambulance staff—presumably sensitized through their in- creased exposure to latex. The commonest reaction is a local reaction on the hands with pruritus and urticaria. Longer exposure results in increased symptoms, including angioedema. In operating theatres where powdered latex gloves are used, repeated glove change leads to an aerosol of allergen in the powder, causing rhino-conjunctivitis. These symptoms can be linked to occupational exposure. Other groups at increased risk of developing latex allergy include children who have undergone

repeated surgery (e.g. for spina bifida). Until the 1980s latex allergy was rare, with only a few case reports. It then became common, especially in healthcare workers, probably because of the increased use of rubber gloves. There were deaths from anaphylaxis due to rectal absorption of allergen from latex rubber catheters for barium enemas. New cases are now rare, fol- lowing the introduction of non-powdered latex gloves. Latex allergic patients require strict latex avoidance when under- going medical procedures or surgery; latex-free equipment must be used. Most catheters and many other medical products are now non- latex, but the vaginal probe used in gynaecological ultrasonography may be covered with a condom and reactions have occurred. It is important to distinguish latex allergy from contact dermatitis due to a type IV reaction to chemicals used in rubber manufacture. This presents with hand eczema, and is diagnosed by a patch test to these chemicals. It is not dangerous and if the patient is admitted strict latex avoidance is not required although contact with rubber should be avoided. Most Trusts have latex policies providing advice on latex avoidance for patients. Healthcare workers with latex al- lergy are usually able to continue their employment. Differential diagnosis Anaphylaxis may present with collapse and loss of consciousness or severe dyspnoea and cyanosis. It is important to consider myocar- dial infarction, pulmonary embolus, diabetes, or severe asthma. The presence of urticaria or angioedema is helpful. Hypotension is usu- ally accompanied by tachycardia. It is usually straightforward to diagnose the disorder (e.g. asthma or anaphylaxis). The issue is to determine the cause: whether allergy is playing a role and if so which allergy(-ies). Clinical investigation Acute reactions Tryptase In acute severe reactions, including anaphylaxis, it is valuable to take a timed blood sample for serum tryptase. This is elevated transiently, so the sample should be taken within 1 to 2 h of onset. In very severe anaphylaxis it may still be elevated up to 4 h, so if the optimal 1–2 h time point is missed a later sample can still be useful. This confirms mast cell activation and degranulation. Tryptase is often but not al- ways elevated in anaphylaxis.
Later investigation A detailed allergy history is the key. Knowledge of allergens, the disorders, and symptomatology they cause is essential. Tests do not substitute for this; they can only be used as an adjunct to history, to confirm or refute suspected allergy. Specific IgE: Skin prick tests or serum-specific IgE assays Tests for specific IgE are best done by skin prick testing, but can also be measured in serum. The latter is commonly referred to as the radio-allergosorbent test (RAST) after the original test although this is now available as other assays including enzyme-linked immuno-sorbent assay (ELISA). Skin prick tests are superior, but mainly available in specialist settings. The problem with these tests is interpretation, as many subjects have positive tests without symptoms. To aid interpretation, 95% predictive levels have been identified for some allergens, levels above which there is a high probability of clinical allergy. Although helpful, this does not resolve the problem, as for individual allergens, different predictive values are proposed depending on the cohort of patients (age, disease, and so on). In addition, there remains a grey area where the test is positive but below the predictive level, where some patients are allergic and others not. A simple rule of thumb is that about half of those with positive tests in the low/moderate range are sensitized but not allergic, but this varies with the population being studied. The key is the clinical history as test results in isolation can be misleading. If the reaction is non-IgE mediated, tests for specific IgE are ir- relevant. For most of these reactions there are no confirmatory la- boratory tests. This applies to some drug allergies (e.g. NSAIDs and aspirin), where the reaction is a result of leukotriene generation. Intradermal tests There are performed by specialists, and can be useful in drug allergy to detect specific IgE when the skin prick test is negative or in T-cell mediated reactions. Challenge tests These are useful if the diagnosis cannot be reached from history and skin tests. They are used mainly for diagnosis of drug and food allergy, and to determine if

resolution has occurred. Challenge testing should only be undertaken in a specialist allergy unit because of the risk of anaphylaxis. Criteria for diagnosis For allergic disorders where there is a trigger, whether IgE-mediated or not, diagnosis is made by history and confirmatory tests, which may be skin prick tests (or serum-specific IgE), intradermal test, or challenge. For idiopathic anaphylaxis, angioedema, and so on, diag- nosis is made by exclusion of other causes. Treatment Allergen avoidance Treatment involves pharmacotherapy and avoidance of allergen or trigger. In the case of food or drug allergy, avoidance can completely

4.5 Allergy 377 stop further acute episodes or chronic disease (e.g. eczema). Avoidance of animals will significantly reduce or prevent allergic asthma and rhinitis. House dust mite avoidance measures can only reduce, not eliminate, exposure, but can impact on symptoms. Drug avoidance is easier to achieve, but patients need education on over-the-counter medication and on drug groups to avoid. Drug al- lergy should be recorded in medical records. For some foods, avoid- ance is difficult to achieve because the food is an ingredient, often hidden, or listed under an obscure name. Patients therefore need de- tailed advice. However, data from large studies on nut allergy shows that if patients receive education on avoidance, significant reduction in further episodes with a 60-fold reduction in severe attacks can be achieved (Fig. 4.5.4). In contrast, if the advice is ‘just avoid nuts’, fur- ther reactions because of inadvertent ingestion are frequent. Pharmacotherapy Key drugs are nonsedative antihistamines (quick onset with once daily dosage) and topical corticosteroids, as nasal sprays, inhalers, and creams. Larger than standard doses of antihistamines may be required for difficult urticaria. For allergic rhinitis and conjunctivitis, step-up therapy tailored to severity is used, as for asthma. Mild disease can be controlled by oral antihistamines, and moderate by nasal cortico- steroid ± oral antihistamines. Steroid nasules or nose drops alone or alternating with nasal steroid sprays are used in severe perennial rhin- itis and nasal polyps. Cromoglicate or nedocromil eye drops are used long term, occasionally with steroid eye drops for short periods for severe conjunctivitis. Intramuscular adrenaline is the drug of choice for anaphylaxis, followed by intravenous chlorpheniramine and hydrocortisone. Further treatment with oxygen, nebulized salbutamol, and intra- venous fluids may be required. If an acute reaction is evolving, with generalized urticaria and angioedema, but not clearly anaphylaxis, treatment can be begun with intravenous chlorpheniramine and hydrocortisone. Patients who have suffered anaphylaxis should carry an adrenaline autoinjector and be trained in its use, unless the allergen can be absolutely avoided. Tongue swelling, depending on severity, requires oral antihista- mine, soluble oral prednisolone, or intramuscular adrenaline. Early self-treatment with these drugs usually controls the attack. Montelukast is helpful as an adjunct to other therapy in certain subgroups with asthma, angioedema, urticaria (including exercise induced), and nasal polyps with rhinosinusitis. Immunotherapy Allergen immunotherapy, or desensitization, is a different approach to treatment. It alters the immune response, down-regulating and ideally ‘switching off’ the allergy. Conventionally it is given sub- cutaneously. Incremental doses of allergen are given at 1 to 2 weekly intervals until the top dose is reached, then maintenance therapy for 3 years. For pollen, shorter courses of preseasonal treatment are avail- able. Sublingual immunotherapy is increasingly used for a range of allergens in most of Europe and is licensed for pollen in the United Kingdom. A tablet is taken daily for 3 years and only the first dose has to be given in hospital, making it more accessible to patients. There are fewer side effects than with subcutaneous immunotherapy. Cochrane meta-analysis shows immunotherapy is effective for seasonal allergic rhinitis (subcutaneous) and allergic rhinitis due to pollen or other allergens (sublingual). Immunotherapy is highly ef- fective for venom anaphylaxis. Issues are patient selection and safety. There is an

incidence of severe allergic reactions to immunotherapy and deaths occurred in the 1980s, so immunotherapy should only be given by specialists with appropriate expertise. Recent data has demonstrated it is possible to desensitize to foods, including peanut, using oral immunotherapy, with efficacy con- firmed in a systematic review and meta-analysis. A licensed prepar- ation is expected soon. Anti-IgE and other biologicals Monoclonal antibody therapy is available for severe asthma and has been shown to reduce repeated hospital admission. Expense and restrictive criteria limit its use. Anti-IgE is also approved for severe urticaria. While giving control this is usually lost on stopping the drug. as this therapy does not affect the natural course of the disease, so repeat courses are re- quired. In both conditions, anti-IgE therapy can transform patients lives. Other biologicals include an anti-IL4/IL13 for severe eczema and anti-IL5 monoclonal antibodies, which target and deplete eosino- phils for use in severe eosinophilic asthma. Health economics There is a significant burden of allergic disease, but much of this is not diagnosed or coded as allergy. The true size of this burden, the cost to the patient or to the health service, is unknown. In the United Kingdom direct health service costs for managing allergic problems are estimated at over £1 billion/year. However, the failure to diagnose allergy means disease is left unchecked, resulting in unnecessary cost to the National Health Service. Diagnosis of drug and food allergy stops further manifestation of the disease—anaphylaxis, acute allergic reactions, or eczema in a child. Other allergen avoidance leads to con- trol of symptoms and lower drug consumption, again saving cost. Incorrect labelling as allergy also has economic consequences. Only 10% of the 5.9 million people in the United Kingdom la- belled as allergic to penicillin are in fact allergic. Costly alternative antibiotics are prescribed unnecessarily, causing further problems with prolonged hospital stays and increased incidence of C. difficile and vancomycin-resistant enterococcus. Accurate diagnosis in the subset with high or specific antibiotic needs is cost effective. Areas of uncertainty • Requests for allergy tests, usually serum-specific IgE, without al- lergy knowledge to interpret the results is a common source of 0 25 50 75 Index reaction Follow up reaction Severity of reaction % Severe Moderate Mild Fig. 4.5.4 Effect of a management plan in reducing subsequent reactions to nuts. Reproduced from Ewan PW, Clark AT (2005). Efficacy of a management plan based on severity assessment in longitudinal and case-controlled studies of 747 children with nut allergy: proposal for good practice. Clin Exp Allergy, 35, 751–6. With permission from Wiley-Blackwell.

 confusion and often results in the wrong diagnosis being made. This is because a ‘positive’ test does not necessarily correlate with disease. Thus, a positive specific IgE alone, without the history, cannot be assumed to indicate allergy. A common misconception is that the level of specific IgE correlates with severity. There are levels of specific IgE above which clinical allergy is likely. • It is not known if sublingual immunotherapy is as effective as sub- cutaneous immunotherapy, and further studies are needed on its safety profile. • Oral immunotherapy for food allergy is a promising research area with efficacy demonstrated for peanut allergy and licensed prod- ucts expected. • The mechanism of idiopathic allergic-type reactions is not known. Better understanding of mast cell biology is needed. These reac- tions may reflect altered mast cells stability. • There are gaps in the epidemiology of allergy, especially for and drug allergy. Future developments Research into new forms of allergen immunotherapy, including oral im- munotherapy for food allergy, are likely to lead to changes in practice.
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