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journal homepage: [www.elsevier.com/locate/transci](http://www.elsevier.com/locate/transci)Angioedema: Patients experience and treatment relief<sup>☆</sup>Martha Kaeslin, Andreas R. Huber<sup>\*</sup>

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## ABSTRACT

Angioedema is defined as a swelling of the skin, mucosa and submucosa of the respiratory tract. It may also impair the intestinal epithelium and other mucous membranes. It can be potentially life-threatening if the upper respiratory tract is involved. In these cases emergency treatment is often required in particular if the pharynx and larynx are swollen. Beside the well-known etiologies of allergic angioedema, many forms of nonallergic angioedema are known and in the majority of these forms increased plasma and tissue concentrations of bradykinin play a critical role.

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## 1. Introduction

This article is based on an interesting case of angioedema caused by an angiotensin converting enzyme inhibitor (ACEi) taken for treatment of hypertension. The authors would like to sensitize the readers to the fact that angioedema is an established side effect of ACE-inhibitor treatment. In view of the fact that ACEi are very often prescribed for hypertension, heart failure and long-term prophylaxis after myocardial infarction, the prevalence should be quite high. Cough as a well known side effect of ACE inhibitors might well reflect a mild form of angioedema. Taken together, it seems that angioedema caused by ACEi is an underdiagnosed entity.

## 2. Forms of angioedema

Angioedema can be of allergic or nonallergic origin. The principal pathogenetic mechanism of allergy is immunoglobulin (Ig)E-mediated. Allergic angioedema leads to urticaria as a result of degranulation of mastcells. Antigen

activated mast cells or basophils release their reactive mediators such as histamine and cytokines into the environment. These mediators cause different characteristic symptoms of allergy including bronchial constriction and inflammation.

Nonallergic angioedema might be caused by hereditary defects or is disease associated or of iatrogenic origin (Fig. 1), such as induced by angiotensin converting enzyme inhibitor (ACEi), and can be divided into five different types (Table 1), e.g. hereditary angioedema (HAE), acquired angioedema (AAE), RAAS-blocker-induced angioedema (RAE) pseudoallergic angioedema (PAE) and idiopathic angioedema (IAE) [1]. Although first described more than 100 years ago, the pathophysiology, cause, and management of the several types of angioedema are often not completely appreciated by physicians.

## 3. Hereditary angioedema

The classic type of autosomal dominant inherited HAE is a result of a quantitative or functional defect of the plasma inhibitor of the first component of complement C1 i.e. C1-esterase-inhibitor (C1-INH) caused by different mutations. The C1NH gene has been mapped to Chromosome 11 (11q12-q13.1) (OMIM 606860). An overview of complement activation pathways [2] and a scheme of the inhibition sites of C1-INH [3] are shown in Figs. 2 and 3.

<sup>☆</sup> This case description of a drug-induced angioneurotic edema was presented at the 2nd International Symposium on Defects in Innate Immunity and Inflammation in Zurich, Switzerland, February 2011.

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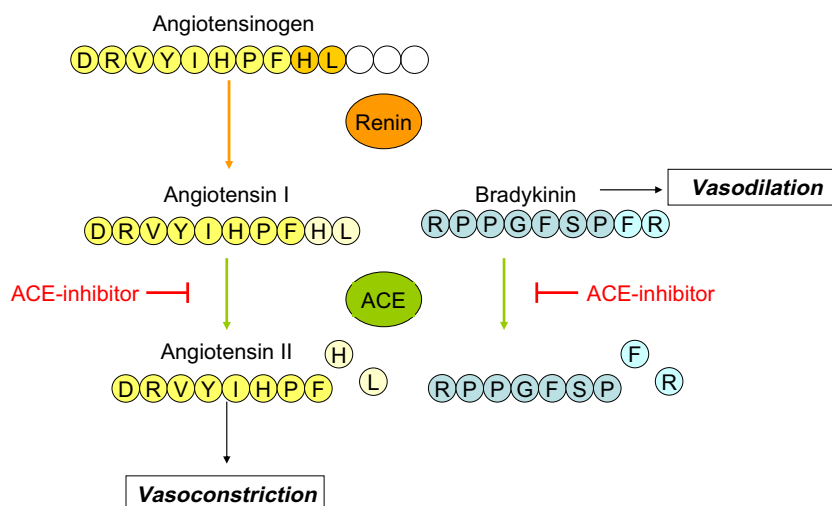


**Fig. 1.** Scheme of ACE-inhibitor function. Through ACE-inhibitor action degradation of Angiotensin I and bradykinin is blocked resulting in decrease of vasoconstriction and increase of vasodilation, respectively.

**Table 1**

Forms of non-allergic angioedema, their major inducing background, mediators and choice of drugs.\*

| Forms of non-allergic angioedema | IAE (idiopathic)                                          | PAE (pseudoallergic)   | RAE (RAAS-blocker-induced)                                                                                                                                                                                                        | HAE (hereditary)        | AAE (acquired)                     |
|----------------------------------|-----------------------------------------------------------|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------------------------|
| Inducers                         | Largely unknown                                           | NSAID                  | – ACE-inhibitors<br>– Renin-inhibitors                                                                                                                                                                                            | C1 inhibitor-deficiency | – Lymphoma<br>– Autoimmune-disease |
| Mediators                        | Unknown                                                   | Cysteinyl-leukotrienes | Bradykinin                                                                                                                                                                                                                        |                         |                                    |
| Drug treatment                   | – Corticosteroides<br>– Epinephrin<br>– $\beta$ -Mimetics |                        | – Bradykinin receptor inhibitor (Icatibant)<br>– Human C1 inhibitor (fresh frozen plasma or concentrate)<br>– Androgens (Danazolom)<br>– Discontinuation of drug and treatment of underlying illness in RAE and AAE, respectively |                         |                                    |

\*Abbreviations: see text.

In patients with HAE, heterozygous C1-INH deficiency results in autosomal-dominant inheritance with an incidence of ~1:50,000. Further, no differences between ethnic groups or sex have been found. HAE leads to uninhibited tissue bradykinin formation. The disease is recognized biochemically by a low plasma C4 level and low quantitative or functional C1 inhibitor concentration.

#### 4. Acquired angioedema

Angioedema caused by a C1 esterase inhibitor deficiency can also be acquired in several clinical settings, including lymphoma and autoimmune connective tissue disease, where C1 inhibitor levels are depressed [4].

Patients with connective tissue disorders such as systemic lupus erythematosus or patients with carcinoma [5,6] can show acquired C1 inhibitor deficiency. These patients like patients with the hereditary form, will respond to concentrated C1 inhibitor, fresh frozen plasma, bradykinin receptor inhibitors or androgens.

A second form of C1 inhibitor deficiency results from the synthesis of an autoantibody directed to C1 inhibitor it-

self [7,8]. These patients also have low levels of C4, C1q, and C1 inhibitor protein and function.

#### 5. Idiopathic angioedema

Generally the term idiopathic is used to describe a condition which is triggered by no obvious reason. Treatments for the condition are basically aimed at symptom relief. Idiopathic chronic angioedema is also usually accompanied by urticaria, but can occur without hives. An autoimmune process leading to dermal mast cell degranulation could be an explanation for this kind of “allergic” angioedema.

#### 6. Pseudoallergic angioedema

Many nonsteroidal antirheumatica may lead to a pseudoallergic reaction. Pseudoallergic reactions are non-immunologic as they are related to COX-1 inhibition. They can be elicited by any non steroidal anti inflammatory drug (NSAID) that inhibits COX-1. Examples for some nonselective NSAID are Aspirin (acetylsalicylic acid) and Ibuprofen

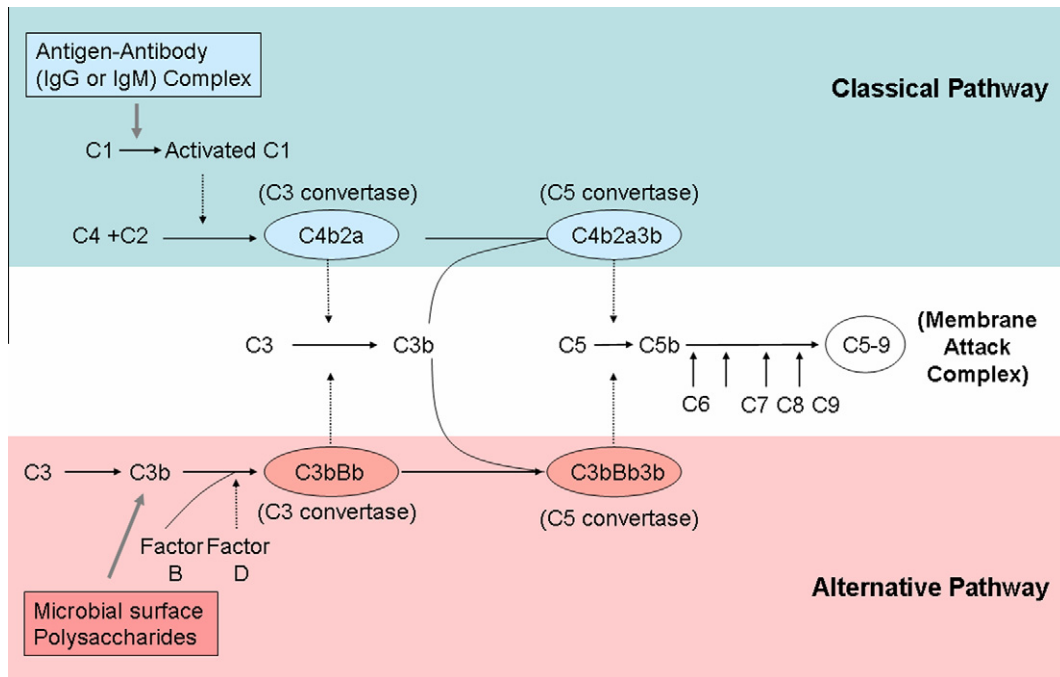


**Fig. 2.** Overview of complement activation pathways. The classical pathway is initiated by C1 binding to antigen–antibody complexes, and the alternative pathway is initiated by C3b binding to various activating surfaces, such as microbial cell walls. Both pathways converge and lead to the formation of the membrane attack complex.

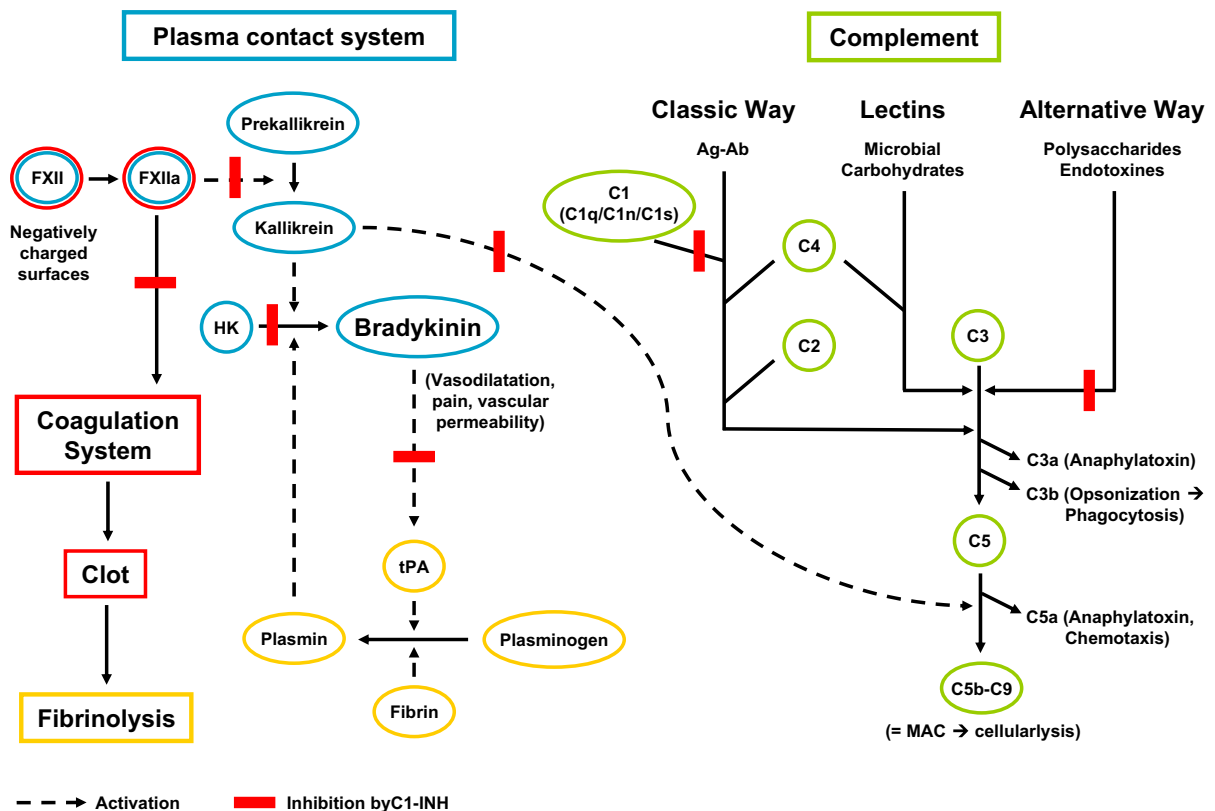


**Fig. 3.** Simplified scheme of complement systems, plasma contact system and inhibition-sites of C1-INH.

(iso-butyl-propanoic-phenolic acid). The precise Zmechanism for a pseudoallergic reaction has not yet been established.

## 7. RAAS-blocker induced angioedema

Drugs which inhibit the Renin–Angiotensin–Aldosterone-System are so called RAAS-blockers. Among the most important compounds, from a medical point of view ACEi are widely used. ACEi act through two distinct pathways. Firstly, they suppress the formation of Angiotensin II from Angiotensin I, Angiotensin II being responsible for vasoconstriction, leading directly into elevated blood pressure (Fig. 3). Secondly, they act on bradykinin: in fact, ACE is responsible for degradation of bradykinin into enzymatically nonactive peptides. Bradykinin is a nonapeptide hormone of the Kinin-group causing blood vessels to dilate, and therefore lowering blood pressure. Bradykinin is a potent endothelium-dependent vasodilator, causes contraction of non-vascular smooth muscle, increases vascular permeability and is also involved in the mechanism of pain; bradykinin is also responsible for natriuresis contributing to a drop in blood pressure through water excretion. Bradykinin is now thought to be responsible for dry cough in some patients taking ACE inhibitors. This refractory cough is a common cause for discontinuation of ACE inhibitor therapy. Bradykinin overexpression may lead to an enhanced permeability of blood vessels, accelerating edema formation of tissues. ACE inhibitor induced angioedema is unaccompanied by hives or urticaria. Additional factors to induce an ACE inhibitor induced angioedema are race and gender; men of African origin are more susceptible to RAAS angioedema than others [9].

## 8. Case report: RAAS-blocker-induced angioedema

A 56-year-old Caucasian without history of asthma, allergies or other significant diseases was suffering from an angioedema induced by ingestion of the ACE inhibitor Lisinopril®.

Prior to this emergency the patient was in good general health with a preobese body mass index of 26.9. During a cardiological check-up carried out preventatively before a high altitude trekking tour, mild hypertension was diagnosed (RR 145/85). Ten days prior to departure for the high altitude mountain expedition (7600 m) the patient started with ACE inhibitor medication (2.5 mg Lisinopril p.o.p.d.) resulting in a normalization of blood pressure (RR 125/80).

During the expedition there were no side effects recognized such as cough, rash or abdominal pain. Ibuprofen was taken occasionally for headaches. 5 days after expedition rapid onset of cough loss of voice and a mild swelling of the face and tongue were recognized. No urticaria was detectable.

Laryngoscopy showed oedematous cords and an oedematous larynx. Swabs for bacteria and viruses were negative and serum C1-INH and C4 were at normal levels. As a therapeutic intervention the patient was given a Bradykinin-B2 Receptor Antagonist (Icatibant®). A significant amelioration of the symptoms was achieved already 2 h later.

In this emergent case an ACE inhibitor induced angioedema was diagnosed correctly, thanks to a careful anamnestic evaluation including drugs taken and an adequate therapy was started rapidly.

Whether in this special case the combination of low atmospheric pressure, cold and ibuprofen therapy was of additional importance for the development of angioedema needs to be determined.

## 9. Therapy of RAAS-blocker induced angioedema

In RAAS-blocker induced acute angioedema episodes, antihistamines and corticosteroids are ineffective. However, subcutaneous adrenaline therapy may be helpful. If a patient has serious respiratory obstruction intubation or tracheotomy should be considered. Fortunately, most acute episodes are non-life-threatening. So far, the mainstay of emergency medical treatment is intravenous fresh frozen plasma or C1 inhibitor concentrate [10]. In addition novel drugs actively inhibiting Kallikrein or antagonists of bradykinin receptor 2 seem promising for emergency treatment of angioedema. These novel drugs rapidly minimize the symptoms. Further, there are no concerns about transmission of HIV or Hepatitis or transfusion related acute lung injury as observed with donation of fresh frozen plasma.

Taken together RAAS-induced angioedema needs to be diagnosed correctly, in order to initiate adequate therapy rapidly [11,12]. Antihistaminics and Corticosteroids have no effect and are thus not indicated. New treatments such as the Bradykinin Receptor 2 Antagonist Icatibant (Firazyr®), the Kallikrein Inhibitor Ecallantide (Kalbitor®) and C1-INH concentrates should be available in every emergency room.

## 10. ACE-associated angioedema is most likely under diagnosed

In 2007 15% of the over 15-year-old Swiss population were on treatment against high blood pressure. Assuming a population size of 6,186,711 about 928,000 persons are thus under treatment for hypertension [13]. Because of this large patient collective and the markedly increasing availability of ACE inhibitors against hypertension and treatment of heart failure, increasing case numbers suffering from side effects can be expected. By far the most commonly encountered complaint with the use of ACEi is a dry, non-productive cough. The cause of this cough has never been fully established. However bradykinin which exists in increased concentrations as a direct result of the action of the ACE inhibitors is the most commonly assumed principal mediator. The cough is generally not severe, but can sometimes lead to unnecessary testing and treatment. Very often this symptom is sufficiently severe to prompt discontinuation of ACE inhibitor therapy in up to 20% [14]. Dry cough can also be a first indicator of a later angioedema which 0.3–1.0% of patients consuming ACE inhibitors ultimately develop [15]. In Switzerland where approximately 400,000 patients are on ACE inhibitors this could result in about 2000 angioedema cases per year

**Table 2**

Comparison of ACE inhibitors registered in Switzerland. There are significant differences among various ACE-inhibitors in respect to bioavailability and half-life.

| Substance    | Trade name           | Bioavailability (%) | Half-life (h) |
|--------------|----------------------|---------------------|---------------|
| Captopril    | Lopirin/<br>Tensobon | 70                  | 2             |
| Cilazapril   | Inhibace             | 45–75               | 1–2           |
| Quinapril    | Accupro              | 60                  | 3             |
| Benazepril   | Cibacen              | 28–37               | 11            |
| Enalapril    | Reniten              | 40–60               | 11            |
| Fosinopril   | Fositen              | 25–29               | 12            |
| Lisinopril   | Zestril/Prinil       | 25                  | 10–13         |
| Perindopril  | Coversum             | 75                  | 7–9           |
| Ramipril     | Triatec/Vesdil       | 30                  | 10–16         |
| Spirapril    | Cardiopril           | 40–50               | 30            |
| Trandolapril | Gopten               | 11                  | 16–24         |

and in Germany where about 7 Mio patients are on ACE inhibitors this could give rise to at least 21,000 cases. Of note is that angioedema does not necessarily develop shortly after the beginning of ACE inhibitor treatment. Different reports have emphasized that although a relatively high proportion of angioedema episodes occur during the early part of treatment, serious events can also be observed many months or even years after initiation of ACE inhibitor therapy [14]. A large clinical survey by Beltrami et al. [11] showed that the average ACE inhibitor exposure before the occurrence of angioedema was a full 12 months and remarkably, it took an additional 12 months from the occurrence of the angioedema until the ACE inhibitor therapy was finally discontinued.

Eleven ACE-inhibitors are currently on the market in Switzerland (Table 2). ACE-inhibitors differ in their bioavailability from 70% to 11% after oral treatment [16]. Further, the half-life time differs from 1 to 30 h. These facts can be of great importance during the treatment of emergency patients suffering from angioedema. Additional side-effects are known such as hyperaldosteronism, dizziness and anaemia. Finally, fetopathy is not to be underestimated, because ACEi crosses the placenta in pharmacologically significant amounts. Clear evidence of fetotoxicity when ACE inhibitors are used beyond the first trimester of pregnancy is available [17].

**In conclusion:** ACEi are widely used and have a variety of well known side effects. Among these, angioedema formation seems to be under-recognized despite its potentially life threatening nature and the fact, that 30% of all non-

hereditary angioedema have been associated with ACE inhibitors [18]. Allergic and non-allergic angioedema need to be considered in patients presenting with symptoms of swollen pharynx and larynx. Depending on the final diagnosis, treatment modalities are quite different, e.g. epinephrine and steroids versus bradykinin-receptor antagonists and C1-inhibitor replacement.

## References

- [1] Bas M, Adams V, Suvorava T, Niehues T, Hoffmann TK, Kojda G. Nonallergic angioedema: role of bradykinin. *Allergy* 2007;62:842–56.
- [2] Abbas AK, Lichtmann AH, Pillai S. Cellular and molecular immunology. 6th ed. Elsevier; 2007.
- [3] Petitpierre S, Bart PA, Spertini F, Leimgruber A. Multiples étiologies de l'angioedème. *Revue Médicale Suisse* 2008;3:154.
- [4] Kaplan AP, Greaves MW. Angioedema. *J Am Acad Dermatol* 2005;53:773–88.
- [5] Donaldson VH, Hess EV, McAdams PJ. Lupus-erythematosus like disease in three unrelated women with hereditary angioneurotic edema. *Ann Intern Med* 1977;86.
- [6] Cohen SH, Koethe SM, Kozin F, Rodey G, Arkins JA, Fink JN. Acquired angioedema associated with rectal carcinoma and its response to danazol therapy. *J Allergy Clin Immunol* 1978;62:217–21.
- [7] Jackson J, Simn RB, Whelan A, Feighery C. An IgG autoantibody which inactivates C1 inhibitor. *Nature* 1986;323:722–7.
- [8] Alsens J, Bork K, Loos M. Autoantibody-mediated acquired deficiency of C1 inhibitor. *N Engl J Med* 1987;313:1360–6.
- [9] Gibbs CR, Lip GYH, Beevers DG. Angioedema due to ACE inhibitors: increased risk in patients of African origin. *Br J Clin Pharmacol* 1999;48:861–5.
- [10] Sabroe RA, Poon E, Orchard G, Lane D, Francis DM, Barr RM. Cutaneous inflammatory infiltrate in chronic idiopathic urticaria: comparison of patients with and without anti-FcεR1 or anti-IgE autoantibodies. *Allergy Clin Immunol* 1999;103:484–93.
- [11] Beltrami L, Zingale LC, Carugo S, Cicardi M. Angiotensin-converting enzyme inhibitor-related angioedema: how to deal with it? *Expert Opin Drug Saf* 2006;5(5):643–9.
- [12] Bas M, Hoffmann TK, Kojda G. Evaluation and management of angioedema of the head and neck. *Curr Opin Otolaryngol Head Neck Surg* 2006;14(3):170–5.
- [13] Bundesamt für Statistik, Schweizerische Gesundheitsbefragung; 2007. p. 312–3. Available from: <www.bfs.admin.ch>.
- [14] Weber MA, Messerli FH. Angiotensin-converting enzyme inhibitors and angioedema: estimating the risk. *Hypertension* 2008;51:1465–7.
- [15] Bangalore S, Kumar S, Messerli FH. Angiotensin-converting enzyme inhibitor associated cough: deceptive information from the Physician's Desk Reference. *Am J Med* 2010;123(11):1016–30.
- [16] Fischler MP, Follath F. Vergleichende Evaluation der ACE-Hemmer: Welche Unterschiede sind relevant? *Schweiz Med Wochenschr* 1999;129:1053–60.
- [17] Aronson J. Meyler's side effects of drugs. 15th ed. Elsevier; 2005.
- [18] Hoover T, Lippmann M, Grouzmann E, Marceau F, Herscu P. Angiotensin converting enzyme inhibitor induced angio-oedema: a review of the pathophysiology and risk factors. *Clin Exp Allergy* 2010;40(1):50–61.