- individuals who take certain pharmacological agents.

Vitamin D supplementation

Only few foods are a good source of vitamin D, namely fortified dairy products and breakfast cereals, fatty fish, beef liver and egg yolks. Besides sun exposure, the best way to get additional vitamin D is through supplementation. Traditionally, multivitamins contained about 400 IU of vitamin D, but newer ones contain 800 - 1 000 IU. Two forms of vitamin D are available, namely D_2 (ergocalciferol) and D_3 (cholecalciferol). D_3 is the preferred form, as it is more effective. As it is a fat-soluble vitamin, it should be taken with meals. Corticosteroids can reduce calcium absorption, which impairs vitamin D metabolism. Lipase inhibitors such as Orlistat and cholestyramine may reduce its absorption, and phenobarbitol and phenytoin may increase the hepatic metabolism of vitamin D to inactive compounds and thereby decrease calcium absorption. Newer work has shown that adults may need a vitamin D intake exceeding 2 000 IU per day.[12]

Measurement of vitamin D

Vitamin D status is measured by 25-hydroxyvitamin D, as levels of 1,25-dihydroxyvitamin D in deficiency states may be normal, high or low. 25-hydroxyvitamin D is a better indicator of the body's vitamin D reserve and is therefore the analyte of choice to measure in the laboratory.[1] For the purpose of this article, we will be referring to the measurement of 25-hydroxyvitamin D to avoid confusion. The suggestion that vitamin D is associated with disease conditions other than calcium dysfunction, as mentioned above, has led to an increase in demand for the measurement of vitamin D.

Vitamin D can be measured separately as vitamin D_2 or D_3 or as a total value. Vitamin D_3 is mainly endogenously derived, and accounts for approximately 95% of vitamin D, whereas vitamin D_2 is derived from food sources and is usually the minor fraction. However, with supplementation, vitamin D_2 is given and assays that only measure vitamin D_3 may underestimate the efficiency of treatment.[13] Assays that mainly measure a specific fraction can thus mislead the physician. The most important value is the final total value, as this represents the total amount of 25-hydroxyvitamin D (D_2 and D_3) in the blood.

Previous assays were problematic, with >30% interlaboratory differences in results shown in 1995.[12] This variation in results at that time led to Heaney stating in 2000 that 'when ordering and interpreting serum 25-hydroxyvitamin D concentration, the physician needs, in virtually all cases, to ignore the laboratory's published reference range…'[14] Improvements in assay standardisation and the introduction of new automated assays for vitamin D led to an improvement in interlaboratory difference to 15% in 2011.[12]

Laboratories face various problems when measuring 25-hydroxyvitamin D, which exists in various molecular forms and is bound to vitamin-binding protein.[12,15] Reference ranges used by the laboratory depend on the reference population used, which in turn depends on season, altitude, latitude, age, skin colour and skin pigmentation, as all these factors may affect vitamin D levels.[2] The value also depends on the assay used, as standardisation has not yet been achieved due to methodological variability. This means that values may not be comparable between laboratories and may confuse clinicians.

Conclusion

Recent literature has highlighted the nonskeletal effects of vitamin D, which has led to an increase in demand for vitamin D assessment from the laboratory. This has forced the development of more rapid automated assays for the determination of vitamin D levels and attempts at standardisation of the assay to enhance clinician satisfaction and reduce confusion. As researchers discover more associations between vitamin D levels and disease, the demand for vitamin D measurement in clinical practice is bound to increase even further. It is therefore important that the clinician understands the basic physiology that can influence laboratory assays as well as the pitfalls of the assays to aid with interpretation of results.

References available at www.cmej.org.za

Investigation of immediate-onset IgE-mediated food allergy

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It is important to differentiate between food allergy and other causes of adverse reactions to food because patients with severe immediate-onset IgE-mediated food allergy are at risk of developing anaphylaxis that may cause death (Fig. 1).

Up to 35% of the population in Western countries self-report 'food allergies', but the true prevalence is probably between 3% and 6% in children and 1% and 4% in adults.[1] Approximately 90% of documented cases of food allergy in the USA are caused by a relatively small number of foods that comprise cow's milk, egg, soy, wheat, peanut, tree nuts, fish and shellfish. Food-induced anaphylaxis is caused mainly by peanut, followed by tree nuts, fish, cow's milk and egg.

Laboratory investigations

Current food allergy guidelines emphasise that a true diagnosis of immediate-onset IgE-mediated food allergy requires a positive history of clinical allergy to a specific food as well as a positive allergy test that matches that history.[2-4]

Any investigation into food allergy has to commence with a detailed allergy-focused history and examination, followed by a selection of appropriate tests to confirm or exclude allergy. It is important to distinguish between sensitisation (the presence of allergen-specific IgE antibodies) and allergy (the presence of sensitisation plus clinical signs and symptoms of allergic reactivity). Skin-prick tests (SPTs) and blood allergen-specific IgE tests measure sensitisation, while oral food challenge tests measure clinical reactivity.

Skin-prick test

A SPT is an indirect qualitative measurement of IgE sensitisation. A positive SPT is triggered by specific

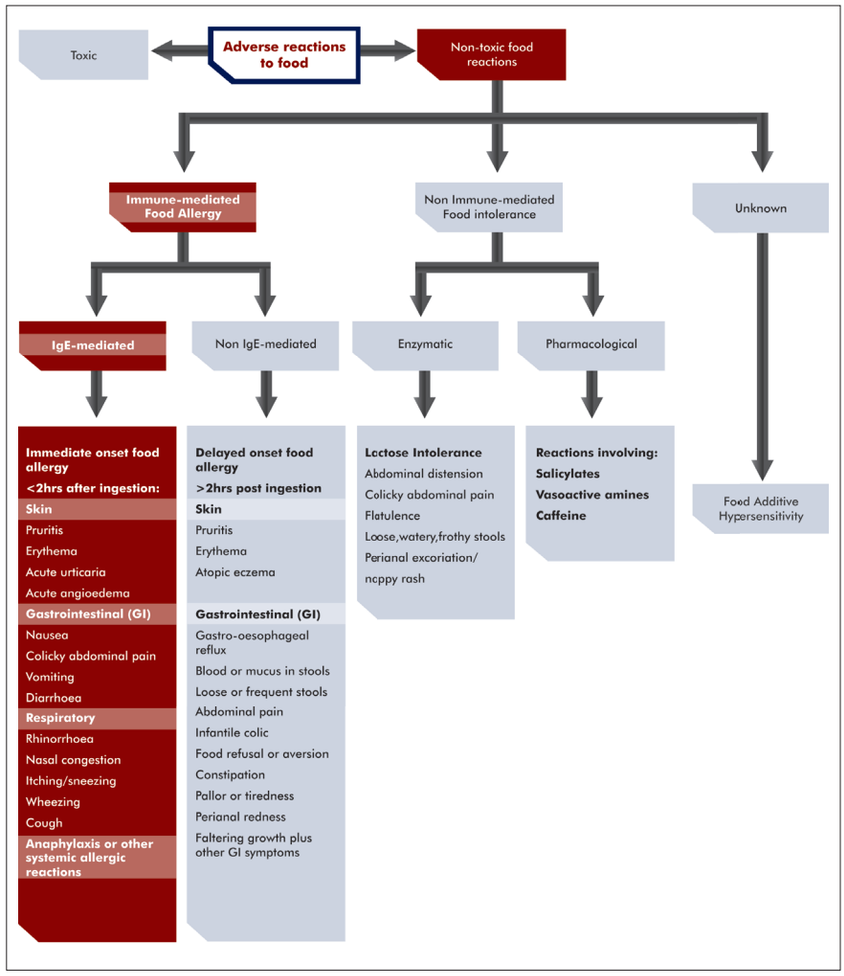

Fig. 1. Adverse reactions to food.

allergen-induced cross-linking of IgE antibodies on sensitised mast cells and the subsequent release of histamine that causes an itch, a flair and a wheal response at the prick site. Although this immune-mediated mechanism is by far the most potent trigger of mast cell degranulation, there are other non-immune mediated triggers that have similar effects. SPTs are sensitive (few false negative results), but they lack specificity (many false positive results). A SPT only has a 50% positive predictive value (PPV) for the diagnosis of food allergy in the absence of a clear history. Interpreting SPTs without a proper evaluation of the supporting history often leads to the over-diagnosis of food allergy.

Certain constraints need to be considered before ordering a SPT. Medications that inhibit the typical histamine reaction should be stopped (Fig. 2). SPTs cannot be performed in patients with dermatographism, or when there is extensive atopic dermatitis or eczema. SPTs should not be selected as first-line tests if there is a history of severe reactions to specific foods, because of the risk of allergen-induced anaphylaxis during the test. None of the former constraints applies to allergen-specific IgE (sIgE) blood tests.

Allergen-specific IgE

The acronym RAST (radioallergosorbent test) is still erroneously used to refer to new-generation sIgE tests, which provide a better measurement of allergen-specific IgE antibodies than RASTs. A positive blood test indicates that specific antibodies are/have been made to a specific food antigen. It confirms sensitisation of the individual, but not necessarily allergy, because <50% of sensitised individuals develop signs and symptoms of allergy during their lifetime. A positive diagnosis of IgE-mediated food allergy requires evidence of both sensitisation and clinical reactivity; a positive sIgE alone cannot confirm allergy in the absence of a clear history of allergy to that food.

sIgE is reported in quantitative units. This allows manipulation of cut-off points to improve the diagnostic specificity of sIgE; the higher the chosen diagnostic cut-off level, the more likely the diagnosis of allergy becomes. Diagnostic cut-off points with a 95% PPV for allergy have been determined for a number of the most important food allergens. They are recommended for use when properly validated (Fig. 3).[1] Unfortunately, such cut-off points are not available for other allergens. It should also be borne in mind that >50% of patients will have sIgE values that are <95% PPV cut-off points; their diagnoses will rely on the supportive history and oral food challenge data.

Although sIgE is generally, but not invariably, less sensitive than SPT, current guidelines indicate that negative tests can be used to rule out allergy in most patients. In instances where sIgE and SPT results are both negative and where the history of allergy is highly suggestive, oral food challenge (OFC) tests have to be done to exclude allergy with more certainty.

Oral food challenge test

The double-blind placebo-controlled food challenge (DBPCFC) is still the gold standard for the diagnosis of food allergy; all allergy guidelines emphasise its importance and encourage its use.[2-4] A DBPCFC is recommended to confirm a diagnosis of food allergy in all instances where there are no reliable 95% PPV diagnostic cut-off points and where the history of allergy is equivocal. A DBPCFC is also indicated if there is a clear mismatch between history and laboratory data. It is costly and time consuming and very few centres in South Africa are equipped to do DBPCFCs routinely.

Single-blind placebo-controlled food challenges (SBPCFCs) and open food challenges are more readily available, but unlike DBPCFCs they do not eliminate

Abstention Period	Drugs that Inhibit Skin Prick Test Reactions
No Abstention	Low dose inhaled and short term corticosteroids generally don't suppress the wheal and flare reaction, although larger doses may do so
1 Day	Histamine H2-receptor antagonists e.g.Cimetidine (Tagamet) or ranitidine (Zantac) have a limited inhibitory effect
2 Days	1st generation antihistamines
3 -10 Days	Non-sedative 2nd generation antihistamines
2 Weeks	Medication with antihistamine properties eg. Anticholinergic agents, phenothiazine and tricyclic antidepressants

Fig. 2. Medications that inhibit the typical antihistamine reaction.

Generic Reference Values for sIgE (KU/L)		95% PPV Cutoff for Specific Foods (KU/L)	
<0.1	= < detect. limit	Egg	>7
0.1 - 0.35	= borderline	Peanut	>14
0.35 - 0.70	= very low pos	Cow's milk	>15
0.70 - 3.5	= low pos	Fish	>20
3. 6 - 17.5	**= positive**	**Soy**	**>65**
17.5 - 50.0	**= high pos**	**Wheat**	**>80**
50.0 - 100.0	**= very high pos**		
> 100	**= extremely high**	Infants (<2 years):	
		Egg	**>2**
		Milk	>5

Fig. 3. Reference values.

clinician and patient bias. Despite this limitation, negative challenges with such tests are considered diagnostic for ruling out food allergy, but the predictive value of positive tests (when allergic symptoms are elicited) is less certain and relies on supportive history and other laboratory test data.

Because of the risk of anaphylaxis in patients with a history of severe allergic reactions, especially in patients with asthma, OFC tests must be conducted in facilities with on-site medical supervision that are properly equipped to deal with medical emergencies. The same applies to SPTs with food allergens.

Evaluation of tolerance

Prolonging avoidance diets unnecessarily is harmful and has a negative impact on patients' nutritional health and psychosocial wellbeing.

The majority of allergic children develop tolerance to cow's milk, egg, soy and wheat between the ages of 3 and 16 years. Approximately 20% of peanut-allergic children will develop tolerance, while <10% outgrow allergy to tree nuts. The likelihood of outgrowing allergy to fish and shellfish is slim and adults who develop any type of food allergy are less likely to develop tolerance than children.

A high initial level of sIgE against food is usually associated with a lower rate of resolution of clinical allergy over time, while declining sIgE levels in children (but not always in adults) is an indication that tolerance is developing. Following quantitative sIgE values over time helps to determine when it is safe to do an OFC test to decide whether an avoidance diet can be stopped. Annual sIgE testing is accepted practice for milk, egg, soy, and wheat, while the test interval can be increased up to three years for peanut, tree nuts, fish and shellfish.

SPTs remain positive long after patients have developed tolerance; they are better suited for initial diagnosis rather than follow-up. Inadvertent sensitisation to specific allergens is also a theoretical possibility during a SPT.

Limitations of traditional diagnostic tests

There are currently no diagnostic tests that can accurately predict anaphylaxis or the severity of future reactions in patients who are allergic to certain foods.

Traditional allergy tests are based on crude natural food extracts that consist of complex mixtures of allergenic and non-allergenic proteins and other molecules.[5] Those based on such extracts are useful screening tests for allergy, but do not discriminate between primary sensitisation to major or minor allergens that have either more or less potential to elicit allergenic reactivity. They also do not discriminate between sensitisation to single or multiple allergens in extract mixtures, and can't establish whether positive reactions are due to cross-reactivity or co-sensitisation to allergenic proteins that are not species specific and that might be very similar to proteins in other foods or pollen to which the patient has been exposed.

Food extracts are very difficult to standardise owing to the complexity of the components in the extracts and the variability of natural products and their endogenous degradation processes. This explains the lack of diagnostic sensitivity and specificity of SPTs and sIgEs that are based on primary food extract mixtures.

Component-resolved diagnostics (CRD) and recombinant allergens

Component-resolved diagnostics (CRDs) and molecular allergology attempt to circumvent the above-mentioned problems. CRDs focus on the use of mono-component sIgE tests that are based on single native allergenic proteins (purified from complex natural food extracts), or on single recombinant antigens (obtained from biogenetically engineered protein fragments that are virtually identical to major IgE-binding epitopes identified on various allergenic food proteins).

Standardisation of recombinant sIgE (,sIgE), either as a single artificial component test or as tests based on mixtures of artificial re-

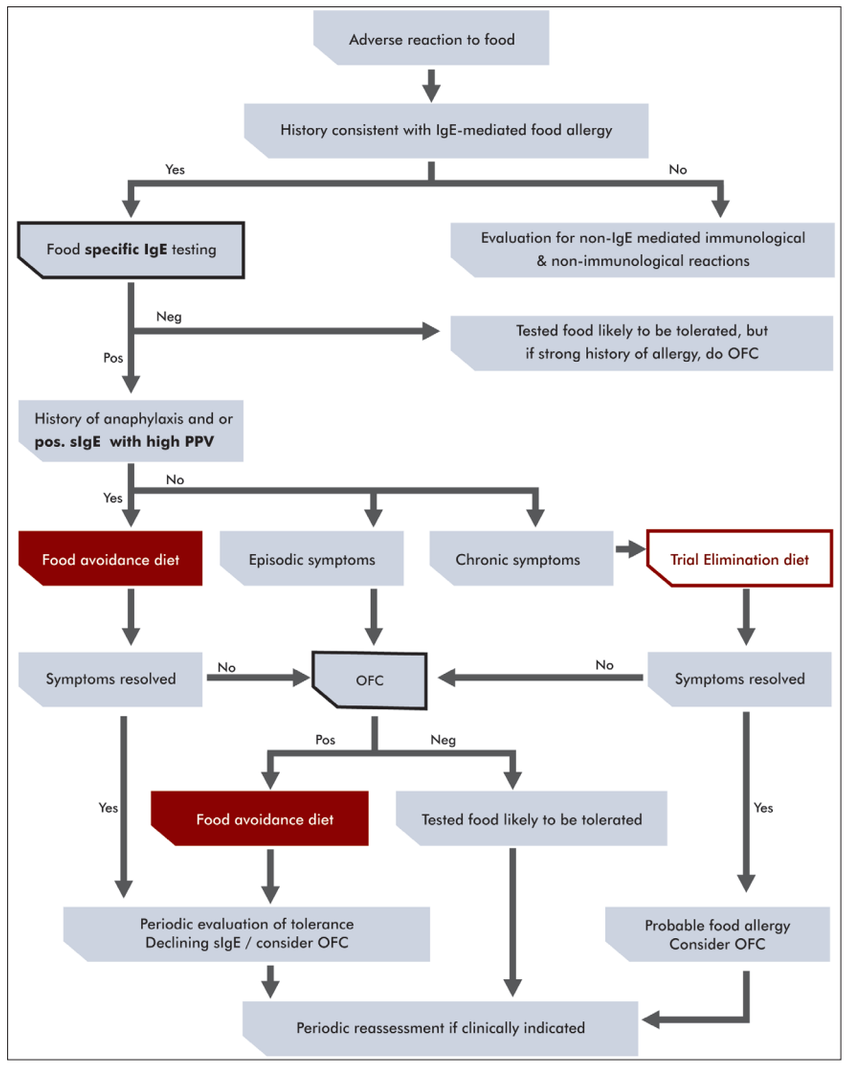

Fig. 4. Investigation of immediate-onset IgE-mediated food allergy.

combinant allergens, is significantly better than tests based on purified native extracts ($_{n}$sIgE) and is clearly superior to tests based on crude food extracts. The development of standardised recombinant allergen $_{r}$sIgE tests has provided clinicians with quantitative tools that can delve more deeply into the precise aetiology of allergy.

Recombinant allergen-based tests have some limitations, however. Individuals are exposed to allergens from natural sources and not to recombinant proteins. They are capable of developing antibodies to a range of different fragments of natural allergens that will not necessarily be present in recombinant allergen-based tests. The use of CRDs and recombinant allergens is currently not recommended to replace, but rather to complement and refine, the results obtained from traditional diagnostic tests.

CRD and peanut allergy

Peanut allergy is the most common cause of food-induced anaphylaxis, but not all peanut-allergic patients have the same risk for anaphylaxis and not all require a strict avoidance diet. Each of the 13 peanut allergens currently identified has its own specific risk- and cross-reactivity profile and each peanut-allergic patient may be sensitised to any one or more of those allergens. This variation explains why some peanut-allergic patients have a higher risk for anaphylaxis and are unlikely to become tolerant, and why some of them will tolerate tree nuts while others will not. A positive peanut recombinant Ara h 2 $_{r}$sIgE has for example become an established risk factor to differentiate patients with true peanut allergy from those who are sensitised but clinically tolerant to peanuts.[6]

CRDs have helped to elucidate the varied nature and risk profiles of other important foods, e.g. tree nuts, fish, milk, egg, soy, wheat, where recombinant allergens play an increasingly important diagnostic role.[5]

Microarrays and comprehensive allergen profiles

A comprehensive allergen profile is required to fully understand an individual's specific risk and cross-reactivity profile. The development of biochip protein-microarrays in combination with multiplexing technology has enabled the simultaneous analysis of large numbers of different allergens on minute samples in a cost-efficient manner. The ImmunoCap ISAC microarray is available in South Africa and provides semi-quantitative measurement of 112 mono-components from more than 50 allergen sources. Nanotechnology benefits paediatric diagnosis, because it requires very little blood to do a comprehensive allergen profile. It is mainly indicated for patients with multiple food and inhalant allergies. Its main drawbacks are onerous validation procedures and the risk of overdiagnosis; it requires specialist knowledge to prevent misinterpretation of the complex results of these tests.[7]

Ongoing research is required to improve the ability of laboratory tests to assess the presence and severity of food allergy and to predict prognosis and resolution of disease.

Summary (Fig. 4)

- Commence investigation of food allergy with a detailed allergy-focused medical history and examination.
- Select the appropriate allergens and co-allergens for sIgE or SPTs to confirm or exclude IgE-mediated allergy.
- Confirm equivocal findings with an OFC test.
- Monitor development of tolerance with sIgE (in children) and confirm with an OFC test.
- Allergy tests should only be undertaken by healthcare professionals who are competent to perform and interpret them.

- SPTs and OFC tests should only be undertaken where there are facilities to deal with an anaphylactic reaction.
- CRDs employing recombinant allergens and comprehensive allergen profiles using microarray nanotechnology offer complementary diagnostic tools for the allergy specialist.

Further reading and references available at www.cmej.org.za

Management of acute bacterial rhinosinusitis

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Rhinosinusitis is one of the most common conditions presenting to clinicians worldwide, and can potentially have an enormous and a devastating socioeconomic impact.[1-7] The majority of infections are viral in origin, and acute bacterial infection occurs in only 0.5 - 2% of cases.[1-5] The dilemma and diagnostic challenge are therefore to distinguish acute viral rhinosinusitis (AVRS) from acute bacterial rhinosinusitis (ABRS).

Definition

Acute rhinosinusitis (ARS) is defined as symptomatic inflammation of the nasal cavity and paranasal sinuses of less than four weeks' duration. Inflammation of the paranasal sinuses rarely occurs without associated inflammation of the nasal mucosa, and the preferred term is rhinosinusitis.[1-7] As the focus of this review is ABRS, please see the reference list – an excellent source for definitions of subacute, chronic and recurrent ARS and any related inquiry.

Pathophysiology[1-8]

Whatever the insult, the underlying problem is sinus ostial obstruction. This is usually due to a preceding viral infection. However, a number of host and environmental factors may predispose an individual to the development of ABRS (Table 1).

AVRS occurs via direct contact with the nasal mucosa or conjunctiva, with symptom onset within approximately 24 hours. Most commonly, rhinovirus, influenza and parainfluenza viruses are implicated. Thereafter, infection spreads contiguously or systemically to the paranasal sinuses. Positive intranasal pressures, as generated during nose blowing, are believed to play a role.

Inflammation ensues that results in nasal hypersecretion, mucosal oedema, increased vascular permeability and impaired mucociliary clearance with transudation of fluid into the sinuses and nasal cavity. This in turn leads to impaired drainage and ventilation of the paranasal sinuses due to obstruction of the sinus ostia. The ostiomeatal complex – the common drainage pathway for the frontal, anterior ethmoidal and maxillary sinuses – is particularly sensitive to this and affected most commonly. Retained, thickened secretions in concert with ciliary dyskinesia, obstructed ostia as well as the antigravitational placement of the ostia, especially of the maxillary antrum, perpetuate the disease process. This leads to the establishment of a favourable milieu for secondary bacterial colonisation and infection.

The normal nasal flora include: coagulase-negative staphylococci, *corynebacteria* and *Staphylococcus aureus*. The organisms (aerobic bacteria) most commonly associated with acute sinusitis are: *Streptococcus pneumonia*, *Haemophilus influenzae* and *Moraxella catarrhalis*. In odontogenic infections, or more chronic cases, microaerophilic organisms and anaerobes may be encountered.

Clinical manifestations and diagnosis[1-4]

Purulent rhinorrhoea, nasal congestion and facial pain or pressure are highly predictive of acute sinusitis, but the distinction between AVRS and ABRS is often difficult. Secondary symptoms such as anosmia, ear fullness, headache and cough may support the diagnosis. The diagnosis of ABRS is made when symptoms or signs

Table 1. Factors that may predispose to the development of ABRS

Host:	Immotile cilia syndrome/ciliary dyskinesia
	Cystic fibrosis
	Immunodeficiency (congenital/acquired)
	Allergy
	Anatomical abnormalities, e.g. severe septal deviation/spurs, nasal polyps, neoplasms, concha bullosa, paradoxically bent turbinates
Environmental:	Infectious agents (viral/bacterial/fungal)
	Irritants: tobacco smoke, noxious chemicals
Iatrogenic/traumatic:	Nasal packing
	Surgery
	Nasogastric tube
	Barotrauma
	Medications
	Foreign bodies

Table 2. Rhinosinusitis initiative (RI) guidelines

Major symptoms	Minor symptoms
Purulent nasal discharge (anterior or posterior)	Headache
Nasal obstruction/blockage	Ear pain/pressure/fullness
Facial congestion/fullness	Halitosis
Facial pain/pressure/fullness	Dental pain
Hyposmia/anosmia	Cough
Fever (acute only)	Fever
	Fatigue (malaise)