

Diagnosis and Management of Shellfish Allergy: Current Approach and Future Needs

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Abstract

Purpose of review Shellfish allergy is an increasing health concern worldwide with over 2% of the population affected and higher rates in countries with high consumption. Shellfish includes both crustaceans and mollusks and constitutes one of the major food groups triggering allergic reactions.

Recent findings Shrimp is the best-studied crustacean, in which the major shellfish allergen, tropomyosin, was initially characterized. Nevertheless, several other allergens have been identified and should be considered despite prevalence of sensitization being lower than tropomyosin (e.g., arginine kinase, myosin light chain, and sarcoplasmic calcium-binding protein).

Summary Diagnosis is not always straightforward; due to the conserved nature of most allergens, there is extensive cross-reactivity between different species which hampers proper diagnosis and management. Clinical symptoms can range from mild local ones to life-threatening anaphylaxis, sometimes with cofactor involvement. Currently, there is no available curative treatment besides diet avoidance and treatment of symptoms in case of accidental exposure.

Introduction

Shellfish includes both crustaceans and mollusks. Nevertheless, crustacean allergy seems to be more frequent than allergy to mollusks, and therefore, it has been studied in more detail. Edible crustacean species, such as prawns, shrimps, crabs, and lobsters, belong to the class Crustacea and specifically to the order Decapoda (class malacostraca) (Fig. 1). Arthropods are distinct from edible mollusks, such as oysters, mussels, squid, octopus, and snail, which belong to phylum Mollusca. The close evolutionary proximity of crustaceans to arachnids (e.g., dust mites and spiders) and insects, such as cockroaches, is probably the reason for

common allergens found among them [1, 2]. Prawns constitute a major part of the consumed and farmed species. However, the terms “prawn” and “shrimp” are used interchangeably in research and in the aquaculture and farming industries. Nevertheless, prawns and shrimps belong actually to two different taxonomical classifications with certain anatomical differences [3]. Edible mollusks can be classified into bivalves (mussel, oyster, clam, and scallop), gastropods (snail and abalone), and cephalopods (squid and octopus).

Prevalence and clinical manifestations of shellfish allergy

Exact data on prevalence of IgE-mediated shellfish allergy are scarce mostly due to the lack of well-controlled epidemiologic studies using controlled food challenges for diagnosis. Nevertheless, it seems that the prevalence of shellfish sensitization and allergy is increasing and might exhibit geographical and age-dependent differences, mainly as a result of different nutritional habits, exposure to cross-reactive allergens, and, last but not least, the applied screening technique.

For instance, in 2002, a telephone survey conducted in the USA among roughly fifteen thousand participants revealed that 2% had experienced an allergy to seafood, being almost 5 times more prevalent in adults than in children [4]. In Europe, based on a systematic review of western/northern European studies, the overall pooled estimate for all age groups of self-

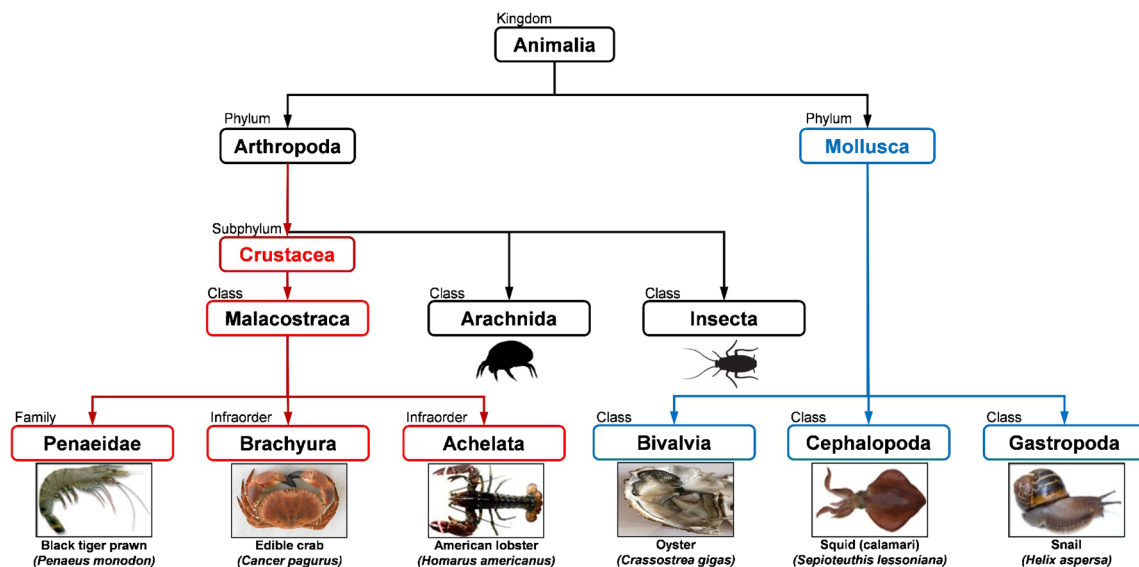


Fig. 1. Classification of edible crustacean and molluscan shellfish species and related invertebrates.

reported lifetime prevalence of allergy to shellfish was 1.3% (95% confidence interval 0.9–1.7%) and the prevalence of food-challenge-defined allergy to shellfish was 0.1% (0.06–0.3%) [5]. In Asia, shellfish is ranked among the most common causes of food allergy with self-reported rates of shellfish allergy around 5% of adolescents in the Philippines and Singapore [6, 7]. In a study between 2003 and 2006, a 39% sensitization rate to shellfish was detected on Singaporean food-allergic children by skin testing [1, 7].

The clinical picture of IgE-mediated shellfish allergy is broad, and most frequently, allergic symptoms have a rapid onset, either through ingestion, direct contact, or inhalation of food vapors. Nevertheless, late-phase reactions up to 6–8 h after ingestion have also been reported [8]. Allergic symptoms range from mild local reactions limited to the oropharynx (oral allergy syndrome, OAS) to systemic reactions; the latter involving the skin and mucosa (pruritus, erythema, acute urticaria, and/or angioedema), nose and eyes (rhinorrhea, sneezing, nasal itching and/or congestion, tearing, burning or itching eyes, redness of eyes), and lungs (cough, dyspnea, wheezes, tightness). In severe cases, patients may present with cardiovascular symptoms including hypotension, shock, and cardiac dysrhythmias. Fatalities have been reported, even by exposure to trace amounts hidden in a kiss [9]. The clinical severity of the reaction might vary within the same individual between episodes, possibly depending on the allergenicity of the species consumed, effect of cooking and boiling, the involvement of cofactors, and the portion of the food eaten [10, 11].

As mentioned before [12], allergic symptoms not only result from ingestion of shellfish but can also be triggered by inhaling (cooking) vapors that contain airborne allergen and by handling food in the domestic and occupational environments [13–15]. As a matter of fact, primary sensitization has been documented through the inhalation of aerosols containing shellfish allergens or even due to swallowing of particles and direct skin contact. Thus, occupational exposure is one of the most important risk factors for the development of shellfish allergy, which seems to be related to the duration and intensity of exposure [16, 17].

Shellfish allergenic proteins: overview

Allergens in various shellfish species are found mostly in the edible meat, although some are also found in the hemolymph, hepato-pancreatic regions, as well as roe. Mostly, they play a role in muscle movement and energy metabolism. Up to 44 different allergens have been identified according to the WHO/IUIS in various species. A summary of the major and minor shellfish allergens is presented in Table 1.

Tropomyosin

Tropomyosin (TM) is the major allergenic protein across all edible shellfish (crustacean and mollusk) species, and it is the best characterized, as it was the first one described in shrimp [20]. More than 80% of crustacean-allergic patients are sensitized to this allergen; therefore, TM-sIgE is frequently used to predict clinical outcomes of shrimp allergy with a high positive predictive value [21, 22]. Belonging to a family of actin-binding proteins, it is involved in muscle contraction and cellular processes in vertebrates and invertebrates [23].

Table 1. Allergenic components in various shellfish species (adapted and updated from [2, 18, 19])

Component	MW weight (kDa)	Allergen nature and function	Heat resistance	Examples (not exhaustive)	Route of exposure	Native conformation
Tropomyosin	34–39	Muscle contraction	Yes	Pen a 1, Lit v 1, Tod p 1, Der p 10, Der f 10, Bla g 7, Per a 7, Hom a 1, Cra c 1, Cha f 1, Mac ro 1, Pen m 2, Lit v 2, Cra c 2, Art fr 2, Der p 20, Bla g 9, Per a 9	Ingestion Inhalation	Dimer
Arginine kinase	40–45	Energy for muscle contraction	No		Ingestion Inhalation	Monomer
Myosin light chain	17–20	Muscle contraction	Yes	Lit v 3, Cra c 5	Ingestion	Monomer
Sarcoplasmic calcium-binding protein	20–25	Regulation of muscle contraction	Yes	Lit v 4, Pen m 4, Cra c 4	Ingestion	Dimer
Hemocyanin	+ 75	Copper containing protein-oxygen carrier	Yes	Bla g 3, Per a 3	Ingestion	Hexamer
Troponin-C	17.7	Muscle contraction/relaxation	Yes	Cra c 6, Bla g 6	Ingestion	Monomer
Triose phosphate isomerase	26–29	Glycolysis	No	Cra c 8	Ingestion Inhalation	Dimer
Paramyosin	100	Muscle contraction	No	–	Ingestion	–
Titin	70	Passive muscle elasticity	Yes	–	Ingestion	Tandem repeats
Fructose 1,6 biphosphate aldolase	39–43	Glycolysis	No	–	Ingestion Inhalation	Tetramer

Pen a, *Penaeus aztecus* (brown shrimp); Lit v, *Litopenaeus vannamei* (Pacific white shrimp); Pen m, *Penaeus monodon* (black tiger shrimp); Art fr, *Artemia franciscana* (San Francisco brine shrimp); Tod d 1, *Todarodes pacificus* (Japanese common squid); Der p, *Dermatophagoides pteronyssinus* (house dust mite); Der f, *D. farinae* (flour mite); Bla g, *Blatella germanica* (German cockroach); Per a, *Periplaneta americana* (American cockroach); Hom a, *Homarus americanus* (American lobster); Cra c, *Crangon crangon* (North Sea shrimp); Cha f, *Charybdis feriatus* (crucifix crab); Mac ro, *Macrobrachium rosenbergii* (giant fresh water shrimp); –, not investigated

For allergen components, see www.allergome.org and www.allergen.org

Nevertheless, it is present in both muscle and non-muscle cells in a highly stable dimeric form. Only invertebrate TMs are allergenic, and they do share high sequence homology. Obviously, this high molecular homology of shellfish tropomyosins translates to significant degrees of IgE cross-reactivity between various shellfish species and shellfish [24–30] and other invertebrates [31–41]. Allergenic TM has generally molecular weights between 33 and 38 kDa, shows high stability to heat treatment [42], retains allergenicity even after cooking and high-pressure processing or other forms of food processing, is water soluble, and easily aerosolized [43, 44]. Based on these physiologic characteristics, TMs are present in cooking broths and vapors [45].

Arginine kinase

Arginine kinase (AK) was the second crustacean allergen discovered and has been described as a minor allergen in several species of shrimp, prawn, and crayfish [46]. Prevalence of sensitization is much lower than TM, although it has been frequently shown to be clinically relevant. AK is an essential enzyme in the regulation of cellular ATP levels highly concentrated in muscle tissue that binds to the muscle protein actin. AK is widely distributed throughout invertebrates, and it has been demonstrated to be implicated in seafood-mite cross-reactivity as well as in insect allergy [47]. Interestingly, it has also been implicated in inhalational exposure and asthma in seafood processing workers [47]. AK, with a molecular weight of 38–45 kDa and usually in a monomeric form, is a heat-labile protein suffering reduced allergenicity after thermal and pH treatment, although IgE binding to AK from heat-treated prawns has been demonstrated [18].

Myosin light chain

Myosin light chain (MLC) belongs to the large EF-hand family of proteins, and it is part of the larger myosin macromolecular complex that makes up the functional muscle protein structure. MLCs are known to be heat and pH stable containing more conformational epitopes rather than linear ones [48]. Further investigation is still required to evaluate the extension of the potential IgE cross-reactivity among different crustacean and other invertebrate species. For instance, a significant homology with Bla g 8 from the German cockroach (*Blattella germanica*) has been observed [49].

Sarcoplasmic calcium-binding protein

Sarcoplasmic calcium-binding protein (SCBP), also a member of the EF-hand calcium-binding protein family, is a 20–24 kDa protein characterized as a crustacean allergen, and it was first identified in white-legged shrimp [50] and later in other species of shrimp [51], prawn [18, 52], crab [53], and crayfish [54, 55]. To date, they have been found exclusively in invertebrates and are thought to act as a functional analogue to vertebrate parvalbumin. SCBPs are heat-resistant and stable under acid/alkali treatment and do not show high conservation, and their sequence identities vary greatly between species with the presence of multiple isoforms. Crustacean SCBPs have two different subunits, α and β , which may form a homodimer or heterodimer that contains four EF-hand domains [56–58]. One study reported that sIgE binding and recognition seemed to be higher in children than in adults [59]. A recent study has demonstrated its utility together with TM, although its prevalence of sensitization is much lower, as a potential biomarker for

predicting clinical reactivity to shrimps [22].

Troponin

Troponins are a 20–21-kDa protein that binds to TM to regulate the contraction of striated muscle. The troponin complex is made up of three subunits: C, I, and T, of which C and I have been shown to elicit sIgE binding. Troponin C binds Ca^{2+} to regulate the movement of TM, and it has been described as an allergen in North Sea shrimp [51], black tiger prawn [60], and American lobster [61]. Troponin I has been identified as a crustacean allergen in narrow-clawed crayfish (WHO/IUIS: Pon I 7). The heat stability of troponins has not been investigated yet. Only 15% of crustacean-allergic patients have been demonstrated to elicit IgE binding to troponin C.

Triose phosphate isomerase

Triose phosphate isomerase (TIM) is a 27-kDa dimeric protein characterized as a shrimp and octopus allergen with its primary function involved in glucose energy metabolism [18, 51, 62]. In addition to crustacean and mollusk species, TIM has been identified as an allergen in cockroach and plants [63, 64]. The cross-reactivity among these species due to TIM has not been investigated in detail yet. Compared to TM and AK, TIM is not an abundant protein and sIgE binding among crustacean allergens ranges from 3 to 23% [18, 51].

Hemocyanin

Hemocyanin is a high molecular weight multi-subunit protein identified as an allergen in shrimps [65, 66] and crabs [67], and it has been implicated in shellfish-mite or shellfish-insect cross-reactivity [65, 68, 69]. It consists of an oxygen transport protein complex that interacts with copper ions from which it acquires its characteristic bluish-green color. Anaphylaxis has been previously reported due to shrimp hemocyanin sensitization, and the utility of this allergen for shrimp allergy diagnostics has been investigated in detail [22, 70]; however, the clinical implications of cross-reactivity due to hemocyanin have yet to be further investigated. At the moment, further investigation is still required to confirm its allergenicity according to the WHO/IUIS guidelines.

Paramyosin

Paramyosin is a major component of the muscle filament, similar to TM, and has been identified and characterized as an abalone [71, 72] and oyster allergen [73]. Paramyosin has also been characterized as a house dust mite (HDM) [74] and anisakis [75] allergen; however the clinical relevance for cross-reactivity has not been thoroughly investigated. Paramyosin shares a very similar structure to TM and sometimes referred to as the water-insoluble TM. It is a heat-labile protein and not yet been identified in crustacean species as an allergen.

Clinical and immunological cross-reactivity: a main issue in diagnosis

Cross-reactivity between shellfish species is a common phenomenon and might involve almost all allergenic components present in shellfish that have been

identified so far. These cross-reactivities can have a significant deleterious effect on the outcome of diagnostics, because of causing positive tests to cross-reacting foods or inhalant allergens (e.g., house dust mite, cockroach) that might not have any clinical implication.

The most well-known pan-allergen is TM, being the major cause for reported clinical cross-reactivity among and between crustacean and mollusks, but also between other invertebrates, including mites, cockroaches, and parasites. It is known that TM has mainly linear IgE epitopes and is of great importance in determining the degree of cross-reactivity between different shellfish species given that it is highly conserved among various crustacean species with amino acid identities reaching 95–100% [2]. Since TM is the major sensitizing source in more than 80% of shellfish-allergic population, the cross-sensitization with or without clinical relevance represents a major issue [76–80].

Within the mollusk group, cross-sensitization to different species of cephalopods, gastropods, and bivalves is often seen in allergic individuals [81], and frequently, these cross-sensitivities are due to sensitization to TMs [82, 83]. Interestingly, crustacean tropomyosin shares a lower sequence identity with mollusk tropomyosin (55–65%). Nevertheless, sensitization to both crustacean and mollusks is common. As a matter of fact, Wu et al. [84] observed by skin prick testing in 70 patients with shellfish allergy that 35.7% were exclusively sensitized to crustaceans, 25.7% exclusively to mollusks, and 38.6% to both.

Cross-sensitization between TM from shellfish and other important allergenic invertebrates, such as dust mites and cockroaches, is remarkably frequent and has been extensively investigated [36, 38, 68, 85–87]. It was demonstrated that sIgE against mite tropomyosin (Der p 10) reacted very strongly to shrimp TM, although this allergen is present in very low concentrations in house dust mites [88]. Because of the in vitro and in vivo cross-reactivity, allergy tests for the diagnosis of shellfish allergy should always be interpreted with caution, especially in HDM-allergic patients. In a study of Thalayasingam et al., it was demonstrated that 26.3% of house dust mite-allergic patients tolerating shrimp showed false-positive sIgE antibodies to a shrimp extract [89]. Noteworthy, reactivity to shrimp has been demonstrated in subjects with HDM allergy, who have never been exposed to shrimps due to religious eating habits [90].

Besides tropomyosin, other allergens may play a role in cross-sensitization. Arginine kinase has been implicated in cross-reactivity to insects, such as moth, spider, and silkworm [91–93]; and hemocyanin may be a potential cross-reactive allergen in crustaceans, dust mites, cockroaches, and mollusks [65, 68, 94, 95]. Recently, a Dutch study group described that shrimp-allergic patients are at risk of food-allergic reactions when eating mealworm. Mealworm (*Tenebrio molitor* L.) and other insects are promising candidates as alternate sources of dietary protein, and TM and AK are thought to be the major allergens causing these cross-reactive food-allergic reactions [96, 97].

Current tools for diagnosis work-up and management of shellfish allergy

Diagnosis of shellfish allergy is challenging because of two main issues. Firstly, it can be difficult to identify the ingested species as there is a wide variety of

consumed species with distinct species farmed in different regions of the world. As commercially available diagnostic methods do not represent this diversity, avoidance of all shellfish is often recommended. Besides that, diagnosis can be hampered because species names are frequently misused or food products are mislabeled.

Second, as mentioned before, the diagnosis of shellfish allergy might be hampered by the high cross-reactivity between different shellfish allergens present in mollusks, insects, mites, and other invertebrates, and the probability of finding positive sIgEs without any clinical implication.

Like for other food allergies, current diagnosis is based on clinical history and additional skin prick testing (SPT) and/or detection of in vitro-specific IgE (sIgE). An oral challenge is still the gold standard for food allergy diagnosis and especially in shellfish allergy might be extremely helpful to correctly diagnose and give dietary advices to shellfish-allergic patients.

In vitro diagnostics: detection of specific IgE antibodies

Detection of sIgE can be done to whole natural extracts prepared from the offending source itself. These tests are easily accessible and are widely available for several shellfish species. However, whole extracts may not always allow standardization of allergen concentrations, and in consequence, quantification of sIgE against allergens in low abundance within whole extract preparations may not be accurate enough, leading to false-negative results.

Therefore, current research is increasingly focused on the use of individual allergens for component resolved diagnosis (CRD) that may improve test sensitivity; in other words, improving the quantitation of sIgE to shellfish allergens of rare abundance or low stability in whole extracts, and on the other hand, increase test specificity with the identification of markers of primary sensitization versus cross-reactivity, but also permitting the possibility to identify sensitization to risk-associated molecules.

Specific IgE to TM, thanks to its high abundance and stability, is picked up easily using heated protein extracts from probably most shellfish species. Nevertheless, multiple studies report that detection of sIgE to TM instead of the whole extract is more efficient in the diagnosis work-up of these patients, mainly because of higher analytical specificity. For instance, Yang et al. [98] observed that the specific IgE against shrimp tropomyosin has a better positive predictive value for clinical reactivity than the prick test or the specific IgE against the whole extract. Later on, Gamez et al. [21] reported similar findings, with a sensitization rate to shrimp and rPen a 1 of 61 and 33%, respectively, among shrimp-tolerant individuals from Spain. However, TM, although a major relevant allergen, does not cover the entire sIgE anti-shrimp response and the additional components (revised in the previous texts) might be necessary to establish correct diagnosis and to evaluate cross-reactivity with other invertebrates [22, 51, 65, 99–101].

The additional value of the shellfish allergens as revised in the previous texts has been studied in several studies. In brief, testing for sIgE to hemocyanin could improve diagnosis of patients allergic to *Macrobrachium rosenbergii* compared to solely testing for sIgE to rPen a 1 [102]. Furthermore, Bauermeister et al. [51] reported that a panel of 6 recombinant allergens from the North Sea shrimp *Crangon crangon* (in particular TM, AK, MLC, SCBP, TpC, and TIM) was

able to correctly identify 90% of the shrimp-allergic individuals analyzed. Similarly, Pascal et al. [22] demonstrated TM to be the main allergenic component positive in 83% of shrimp-allergic patients and 44% of shrimp-tolerant individuals. Regarding the other 9 components tested in this study, it was demonstrated that AK had the highest sensitivity (48%) followed by MLC (38%) and SCBP (34%). Nevertheless, even with the complete allergen panel, the false negativity rate was still 12%.

Recent advances in PCR-based allergen-specific IgE quantification, using serum from a finger prick which is of particular advantage for infant allergy testing, have further improved the sensitivity and specificity to single allergens [41]. On the other hand, whether epitope recognition constitutes a completely reliable technique to document shellfish allergy remains to be further confirmed, although several informative IgE-binding epitopes have been identified [22, 103]. Table 2 provides an overview of allergen sources and components available on the most common platforms for in vitro diagnostics, mostly from native species of the Northern hemisphere. Noteworthy, species from the Southern hemisphere seem to contain considerably different allergens and isoforms [104, 105], posing an additional challenge for reliable diagnostics.

In conclusion, despite all the work done in molecular diagnosis of food allergy, regarding shellfish allergy, still no species-specific allergens have been identified, making it difficult to precisely diagnose allergy to a specific crustacean or mollusk species [3, 42]. If more of the already identified allergens are available for diagnostics, it might be interesting to test one allergen per protein family in order to evaluate sensitivity and specificity of CRD, particularly if TM is not the major implicated allergen. This does not, however, solve the question of potential clinical cross-reactions to closely related shellfish species.

In vivo diagnostics: skin prick testing and oral challenge tests

Skin prick tests (SPTs) with commercial preparations of whole protein extracts are usually used to rapidly evaluate patients with a clinical suspicion of shellfish allergy. However, similar to serum sIgE detection, SPTs do not demonstrate an absolute predictive value for allergy and performances might significantly differ according to the extract used, since the protein composition may significantly vary among species and manufacturers.

Recently, Jirapongsananuruk et al. [106] and Asero et al. [107] showed that SPTs or prick-prick tests with fresh shrimp or home-made shrimp extract do show a somewhat higher sensitivity than a commercial SPT extract. However, like for quantification of sIgE, specificity of SPT was demonstrated to be disappointingly low (0–37.5%) [106].

Food challenge involves administering the suspected food under close control of an allergologist, in order to confirm or rule out an IgE-mediated allergy. Despite some associated risks and the significant time and resource consumption, it is still considered the gold standard in food allergy diagnosis, especially when it is performed double-blinded and placebo-controlled (DBPCFC). Given the benefits of a negative result, the risk that must be assumed is reasonable when it is carried out under the right conditions, i.e., performed in centers that have trained personnel and resuscitation equipment for the control and treatment of possible serious reactions. Importantly, the minimal dose causing symptoms might vary considerably depending on the

Table 2. An overview of IgE-based serological tests available for crustacean and mollusk species

Type of test	Common name	Species	Platform
Whole extract-based serological tests		Crustacean species	
	Crab	<i>Chioecetes</i> spp.	ImmunoCAP ®, ThermoFisher Scientific
	Crayfish	<i>Astacus astacus</i>	
	Langust (spiny lobster)	<i>Palinurus</i> spp.	
	Lobster	<i>Homarus gammarus</i>	
	Shrimp	<i>Pandalus borealis</i> , <i>Penaeus monodon</i> , <i>Metapenaeopsis barbata</i> , <i>Metapenaeus joyneri</i>	
	Crab	<i>Cancer magister</i>	CLA® Allergy Test, Hitachi Chemical Diagnostics, Inc.
	Shrimp	<i>Penaeus</i> spp.	
	Crab	Species not stated	3gAllergy®, Siemens Healthineers
	Shrimp	Species not stated	
	Lobster	Species not stated	
	Crayfish	Species not stated	
		Mollusk species	
	Abalone	<i>Haliotis</i> spp.	ImmunoCAP ®, Thermo Scientific
	Blue mussel	<i>Mytilus edulis</i>	
	Clam	<i>Ruditapes</i> spp.	
	Octopus	<i>Octopus vulgaris</i>	
	Oyster	<i>Ostrea edulis</i>	
	Pacific squid	<i>Todarodes pacificus</i>	
	Scallop	<i>Pecten</i> spp.	
	Snail	<i>Helix aspersa</i>	
	Squid	<i>Loligo</i> spp.	
	Clam	<i>Tapes philippinarum</i>	CLA® Allergy Test, Hitachi Chemical Diagnostics, Inc.
	Blue mussel	Species not stated	3gAllergy®, Siemens Healthineers
	Pacific squid	Species not stated	
	Octopus	Species not stated	
	Clam	Species not stated	
Squid	Species not stated		
Oyster	Species not stated		
Snail	Species not stated		

Table 2. (Continued)

Type of test	Common name	Species	Platform
Component/ allergen-based serological tests	Scallop	Species not stated	
	Shrimp	<i>Penaeus aztecus</i>	ImmunoCAP®, Thermo Scientific
	rPen a 1 (tropomyosin)		
	Shrimp	<i>Penaeus monodon</i>	ImmunoCAP ISAC®, Thermo Scientific
	nPen m 1 (tropomyosin)		
	nPen m 2 (arginine kinase)		
	nPen m 4 (sarcolemmal calcium-binding protein)		
	Anisakis	<i>Anisakis simplex</i>	ImmunoCAP ISAC®, Thermo Scientific
	rAni s 1 (nd)		
	rAni s 3 (tropomyosin)		
	Shrimp	<i>Penaeus monodon</i>	3gAllergy®, Siemens Healthineers
	nPen m 1 (tropomyosin)		

source and thermal processing of the food [108]. Dose-eliciting symptoms vary depending on the study. Decades ago, it was reported that a dose as high as 14–16 g of cooked shrimp might induce first allergic symptoms in shrimp-allergic patients [109, 110]. Nevertheless, in a more recent study, they demonstrated that low doses (1–3 g) of lyophilized cooked shrimp could already elicit symptoms, whereas the eliciting dose for raw lyophilized shrimp was higher (15 g) [106]. There is no standardized protocol for crustaceans yet.

Diagnostic workflow for shellfish allergy

A detailed clinical history is essential for the correct diagnosis of an IgE-mediated shellfish allergy and should address the following several points [111]: extent of symptomatology, causative food(s), timing and chronicity of symptoms, reproducibility of allergic symptoms, quantity of ingested food, processing of the food (raw vs. cooked), required treatment, occupational exposure, and identification of possible risk/predisposing factors (e.g., cofactor(s) like NSAIDs or exercise, underlying atopy, and other (house dust mite) allergies, familial history, coexisting medical problems). To document the clinical suspicion of an IgE-mediated allergy, physicians generally rely upon SPTs and measurement of sIgE antibody levels, considering both whole extracts (skin tests and/or serological tests) and components (serological tests) depending on availability [112]. Finally, if required (i.e., those patients in which traditional tests yield equivocal or negative results), food challenges are indicated.

Nevertheless, it is crucial to take into account the actual limitations of them. For instance, commercial extracts provide good results in case of highly abundant allergens like TM but may show limited value due to false-negative responses in case of heat sensitive- or weak allergens (e.g., MLC, AK, respectively). Prick-by-prick test can be an option in these latter cases seeking for better sensitivity [106].

For serological sIgE testing, both whole extracts, although not for all species consumed in both hemispheres, and certain components are commercially available. Nevertheless, limited sensitivity depending of the relative abundance of certain proteins in whole extracts and not all components described available in all platforms are still important drawbacks. Furthermore, as mentioned before, clinically irrelevant sensitizations must always be considered due to the frequent cross-reactivities described previously. Thus, parallel evaluation of sensitization to other invertebrates, such as dust mites or nematodes, is recommended, especially when anamnesis is not clear. Food challenge tests are indicated when the global allergological evaluation is not conclusive. Nevertheless, it has to be performed under the correct conditions, with the appropriate amount of food (preferably masked), to be sure it is enough to elicit a reaction.

Current treatment and future perspectives

For the moment, in the absence of a cure, strict avoidance of the culprit food remains the cornerstone of shellfish therapy. Traditionally, avoidance of all crustaceans and mollusks has been recommended unless clinical tolerance had been confirmed in a challenge test. However, species-specific allergies have been demonstrated rejecting the idea of shellfish allergy as a pan allergy [4, 106, 113]. With this in mind, the frequently used clinical recommendation that all patients with shellfish allergy should strictly avoid all crustaceans, mollusks, and edible insects may not be absolutely accurate. Larger studies with challenge-documented patients focusing on the understanding of clinical cross-reactivity are still required and absolutely mandatory to better understand and properly manage shellfish allergy and clarify this issue. It is also a general misbelieve that shellfish allergens cross-react with fish allergens. As a matter of fact, the major fish allergen is parvalbumin that cross-reacts with other parvalbumins [114].

In the therapeutic management of shellfish-allergic patients, we should always be aware of the fact that patients may develop symptoms upon exposure to airborne allergens (e.g., cooking vapors) or to hidden allergens. Thus, in some patients, a cofactor may be needed for the clinical expression of sensitization. Because of the cross-reactivity of shellfish with other invertebrates (e.g., house dust mite), the potential therapeutic effect of HDM immunotherapy has been evaluated. Yet, no convincing data have been published; in contrary, shrimp and snail allergies have been described to develop during HDM immunotherapy [115, 116]. Whether the production of hypoallergenic shrimp and/or use of immunotherapy with modified allergens [117, 118] will be able to treat shellfish-allergic patients remains to be established [119].

Conclusion

IgE-mediated shellfish allergy constitutes an important cause of food-related adverse reactions. The clinical presentation of shellfish allergy varies from mild allergic reactions to severe life-threatening anaphylaxis. Over the last two decades, many shellfish allergens have been identified and cloned, among them, invertebrate tropomyosin, arginine kinase, myosin light chain, sarcoplasmic calcium-binding protein, and hemocyanin are the most relevant. In clinical practice, physicians generally rely on quantification of sIgE antibodies and skin testing; however, correct

diagnosis of shellfish allergy is not always straightforward mainly because of uncertainties associated with the correct identification of the offending species by the patient and the low specificity of traditional diagnostics given cross-reactivity issues. In cases where traditional tests yield equivocal or negative results, additional diagnostics like food challenges might be required. Hitherto, avoidance of the offending source and clinically significant cross-reacting species remains the cornerstone of correct treatment and management of shellfish-allergic patients.

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflicts of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

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