



An update on shellfish allergy

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Purpose of review

Shellfish is an important cause of food allergy worldwide, and a major cause of food-triggered anaphylaxis. Despite the wide variety of shellfish, there is considerable serological and clinical cross-reactivity of major shellfish allergens, and accurate diagnosis remains a challenge in the management of shellfish allergy.

Recent findings

Novel minor allergens have been discovered and characterized, and advances in component resolved diagnostics have provided insights into the prevalence of sensitization and their clinical importance in shellfish allergy. The extensive cross-reactivity between tropomyosin of house-dust mite and crustacean shellfish has been postulated to be the cause of a proposed mite-shellfish oral allergy syndrome.

Summary

More studies in food challenge-proven patients are required to establish the true prevalence and natural history of shellfish allergy. Refinement of component resolved diagnostics and testing for minor allergens may be helpful in developing more precise species-specific tests. Further investigation into the role of tropomyosin in house-dust mite and shellfish allergies may provide novel immunotherapeutic approaches for shellfish allergy.

Keywords

cross reactivity, diagnosis, management, shellfish allergy, tropomyosin

INTRODUCTION

Shellfish are one of the most common causes of food allergies in the world [1], and a major cause of food-induced anaphylaxis [2]. Edible seafood comes from three main phyla: mollusca, arthropoda (crustaceans) and chordata (fish) (Fig. 1). 'Shellfish' in general usage typically refers to the two invertebrate groups of crustacean and mollusc species. Edible molluscs can be further divided into the three classes of gastropoda, bivalvia and cephalopoda. Crustacean allergy is more common than mollusc allergy, with prawn or shrimp being the most commonly reported shellfish allergy [3,4].

Prawns are the most commonly consumed shellfish worldwide [5]. The terms 'prawns' and 'shrimp' are often used interchangeably. There are several thousand species of prawns/shrimp. Within the Decapoda class, the term 'prawns' typically refer to species from the Penaeidae group which are usually larger and most commonly implicated in shellfish allergy [6]. Two leading farmed Penaeid species, *Penaeus monodon* (Tiger prawn) and *Litopenaeus vannamei* (Pacific white leg prawn) account for more than 80% of consumed prawn species globally [5]. Another Decapoda family, the Caridea, are usually smaller and more commonly known as 'shrimp'. Despite the interchangeable

nomenclature, Penaeidae and Caridea belong to separate taxonomical crustacean families with distinct anatomical differences [6].

The review aims to outline the epidemiology, clinical characteristics, major and clinically cross-reactive allergens; with a focus on novel aspects of shellfish allergy, including recent developments in identification of novel minor allergens and precision diagnosis.

A PubMed search strategy using the terms 'Shellfish allergy' and 'Seafood allergy' was performed, resulting in 295 articles published between 2008 and 2018, of which 85 were reviewed. The rest were excluded as they were either not written in English ($n = 7$), focused on other allergic diseases apart from

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KEY POINTS

- The later age of onset, low rate of natural resolution, intraindividual variability of reactions and the predominance of perioral symptoms are unique clinical features of shellfish allergy.
- High sequence homology between tropomyosin (the major allergen in shellfish) of different shellfish species, and with house-dust mites and cockroaches accounts for a high rate of serological cross-reactivity, but does not accurately predict clinical cross-reactivity.
- The rate of sensitization to minor shellfish allergens is variable, and the clinical importance of these allergens may vary between different populations.

shellfish allergy ($n=135$), laboratory-based studies ($n=55$), or commentaries on consumer rights, statistics or study methods ($n=12$).

EPIDEMIOLOGY

Table 1 summarizes studies on the prevalence of shellfish allergy over the last 10 years. The prevalence of shellfish allergy is higher in adults than in children. The onset of shellfish allergy is often seen in late childhood or adolescence, in comparison with allergies like milk and egg which present in early childhood [11].

Shellfish allergy prevalence differs between geographical regions and is more prevalent in the

Asia-Pacific region than in Europe and North America. The overall prevalence of shellfish allergy in the western world (USA, Canada and Europe) is about 0.6% (0–9%) [20]. Self-reported rates of shellfish allergy in the western world range from 0.06 to 2% in children, to 1.69–9% in adults in the USA and Canada; and 0.1–5.5% in children to 0.4–2% in adults, in Europe [3]. Challenge proven prevalence studies of shellfish allergy are scarce. The largest such study showed an overall challenge-proven shellfish allergy prevalence of 0.3% in adults in Denmark [21].

The highest prevalence of shellfish allergy is found in the Asia-Pacific region, particularly in adolescents and adults [3,22]. Self-reported rates of shellfish allergy range from 0.9 to 1.19% in children below age 7 years, to 5.12–7.71% in adolescents and adults in Hong Kong, Philippines and Singapore [4,23]. In Latin America, self-reported rates of shellfish allergy range from 1.3% in children 5–13 years to 4% in adults in Mexico, approximating prevalence rates in the United States [12,13].

The differences in prevalence between geographical regions may reflect differences in average consumption of shellfish [5]. Shellfish allergy is also more common in tropical and subtropical Asia-Pacific and Latin America than in temperate Europe and Northern Asia. It has been hypothesized that higher prevalence of house-dust mite (HDM) sensitization in humid, warmer climates is significantly associated with shellfish sensitization and allergy through cross-reactivity between HDM and shellfish

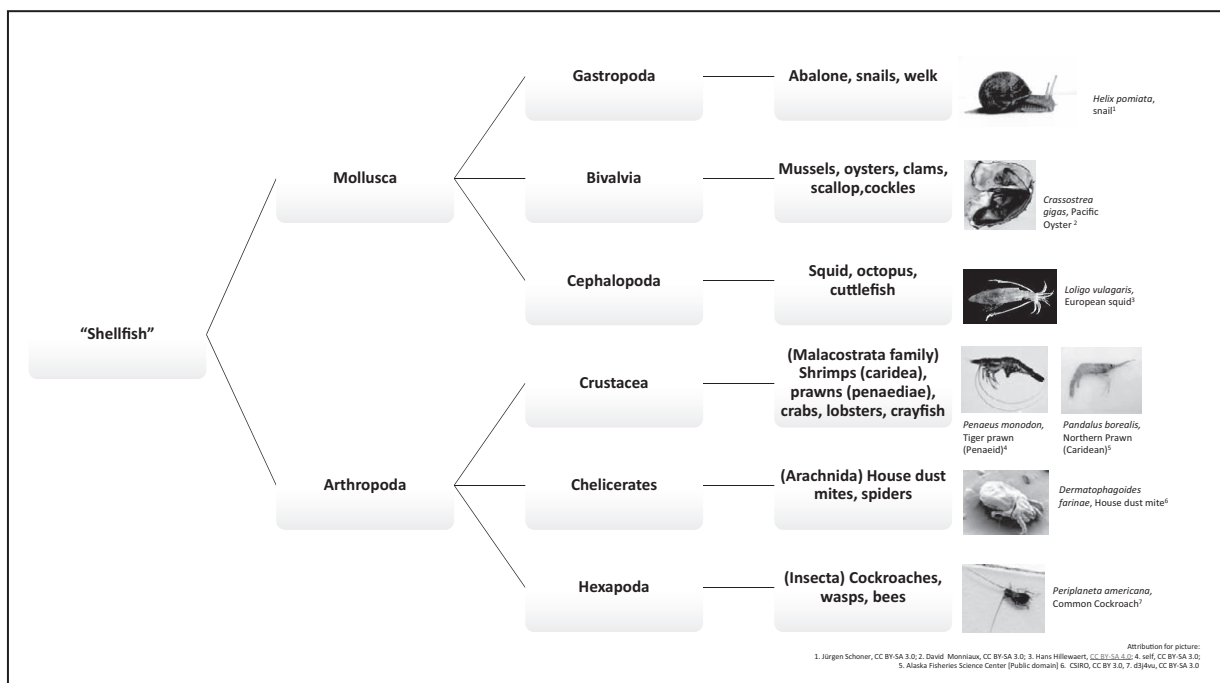


FIGURE 1. Classification of edible crustacean and molluscan shellfish species, and related invertebrates.

Table 1. Global prevalence of shellfish allergy as reported in the last 10 years (2008–2018)

Country	Prevalence (%)	Population (n)	Age (year)	Methodology	Year published	Reference
Europe and North America						
United Kingdom	0.2	1290	18	Report, SPT	2018	Venkataraman <i>et al.</i> [7]
Portugal	0.7	1436	18–80	Report, SPT, slgE	2016	Lozoya-Ibanez <i>et al.</i> [8]
United States	1.3	38 480	0–17	Report, physician diagnosis	2012	Lau <i>et al.</i> [9]
United States	3.9	40 477	>18	Report	2017	Gupta <i>et al.</i> [10]
Canada	1.42	9667	All ages	Report	2010	Ben-Shoshan <i>et al.</i> [11]
	0.5		Children ^a			
	1.7		Adult ^a			
Latin America						
Mexico	1.3	1049	5–13	Report	2016	Ontiveros <i>et al.</i> [12]
Mexico	4	1126	19–37	Report	2015	Barajas <i>et al.</i> [13]
Asia-Pacific						
Korea	0.34	9671	6–7	Report	2017	Kim <i>et al.</i> [14]
	0.89	9756	9–10	Report		
	0.77	5169	12–13	Report		
	1.25	5246	15–16	Report		
Korea	0.5	16 749	0–6	Report	2014	Park <i>et al.</i> [15]
Singapore	1.19	4515	4–6	Report	2010	Shek <i>et al.</i> [4]
	5.23	6498	14–16	Report		
Singapore	0.9	855	3	Report	2017	Tham <i>et al.</i> [16]
Philippines	5.12	11 434	14–16	Report	2010	Shek <i>et al.</i> [4]
HK	1.8	7393	0–14	Report	2012	Ho <i>et al.</i> [17]
Thailand	0.88	452	3–7	Report, SPT, OFC	2012	Lao-Araya and Trakultivakorn [18]
Taiwan	1.1	813	<3 years	Report	2012	Wu <i>et al.</i> [19]
	7.7	15 169	4–18	Report		
	7.05	14 036	>19	Report		

OFC, oral food challenge; slgE, specific IgE; SPT, skin prick testing.

^aExact age not specified.

tropomyosin. These allergens share significant sequence homology [22,24].

The importance of shellfish allergy in the Asia-Pacific region is also borne out by its prominence as a trigger for anaphylaxis, and emergency attendances for allergic food reactions. It is the most common trigger for fatal food anaphylaxis in Australia [2] and the leading food trigger for anaphylaxis in adults in Singapore [25,26], Thailand [27] and Hong Kong [28].

UNIQUE CLINICAL FEATURES OF SHELLFISH ALLERGY

The age of onset of shellfish allergy is often in late childhood or adolescence [11]. The clinical features of IgE-mediated shellfish allergy are similar to that of other allergenic foods. They are typically immediate in onset, although rare late-phase reactions have also been reported [29]. The severity of the

reactions is often variable even within the same individual, and may be influenced by species-specific reactions, food preparation methods, the part of shellfish consumed, and the presence of cofactors (such as alcohol, exercise, NSAIDs) [30–32]. Shellfish is a well known food trigger for food-dependent exercise-induced anaphylaxis, in which exercise is a mandatory cofactor for the occurrence of anaphylaxis [33].

Although severe reactions have been reported with trace amounts [34], crustacean allergy appears to have a high threshold of reactivity. Up to 24% of patients in Singaporean and Thai prawn allergic cohorts reacted only at the top dose of 80 g of prawn (~5–6 large prawns) [35,36].

An interesting clinical feature of shellfish allergy is the predominance of perioral symptoms in certain regions. Particularly in the Asia-Pacific region, the most common manifestation of shellfish allergy is

mild symptoms confined to the lips and oral mucosa [35,37], akin to the oral allergy syndrome (pollen-food) described in subjects primarily sensitized to an aero-allergen, who experience perioral symptoms with consumption of cross-reactive fruits and nuts [38].

Other unusual manifestations of shellfish allergy have also been reported. In a subgroup of US shellfish allergic adult cohort, eight patients reported isolated gastrointestinal symptoms with no systemic involvement [39[■]]. The authors hypothesize that these patients had a form of adult-onset food protein induced enterocolitis syndrome with shellfish. Further investigations are required to establish the mechanisms involved in these reactions.

The natural history of shellfish allergy has not been extensively investigated – it is likely to be persistent with low rates of development of tolerance. A study of self-reported resolution of shellfish allergy in a small cohort of shellfish allergic patients found a resolution rate of 3.6% over 5 years [40[■]]. However, a recent study from Thailand which repeated a second oral prawn challenge after 10 years in a small subgroup ($n = 14$, 23% of original cohort) of challenge-proven prawn-allergic subjects found that 50% passed the repeat challenge, suggesting that the development of tolerance may be more common than previously assumed [41[■]].

CLINICAL CROSS-REACTIVITY

A common perception is that all patients with shellfish allergy should avoid all shellfish, as the risk of pan-shellfish cross-reactivity is high. However, some may be allergic to crustaceans but tolerate molluscs, or exhibit species-specific allergy [42,43]. A population-based USA telephone survey on self-reported shellfish allergy found that only 38% were allergic to more than one crustacean species, 49% were allergic to more than one molluscan species; and only 14% reported both crustacean and mollusc hypersensitivity [42]. There is also significant heterogeneity in mollusc allergy as only 15% of patients are allergic to both cephalopods and bivalves, suggesting that pan-mollusc allergy is the exception rather than the rule [44].

Species-specific crustacean allergy was shown in a Thai cohort which demonstrated mono-allergy to either *Macrobrgiiium rosenbergii* (Caridean shrimp) or *P. monodon* (Penaeid black tiger prawn) [36]. Another Singaporean cohort demonstrated species-specific allergy to either *P. monodon* or *L. vannamei*, two closely related Penaeid prawn species [35].

Several studies have shown high rates of IgE cross-reactivity between crustaceans and molluscs (up to 90%) with skin prick testing (SPT) [43]. Cross-sensitization rates appear to be highest within the crustacean group, followed by molluscs, and then

cephalopods [43,45]. This serological cross-sensitization does not correlate as closely with clinical cross-reactivity, and is therefore unreliable for diagnosis [43].

ALLERGENS

Tropomyosin

Tropomyosin, a skeletal muscle protein, is a pan-allergen in invertebrates [46]; and the major allergen in all edible shellfish [47]. The majority of prawn allergic patients demonstrate positive IgE binding to purified tropomyosin [48,49]. Tropomyosin's alpha-helical coiled structure is highly stable and retains its allergenicity despite thermal and high-pressure processing [30,50].

Tropomyosins of prawns, lobsters and crabs share between 91 and 100% sequence homology [22], which explains the significant degree of IgE cross-reactivity between various shellfish species. Sera from shrimp allergic subjects demonstrated similar IgE-binding reactivity to epitopes from shrimp tropomyosin (Pen a 1 – *Penaeus aztecus* shrimp) and their homologous sequence in lobster tropomyosin (Hom a 1 – *Homarus americanus* lobster) [47].

Tropomyosins of HDM and cockroaches also share a high sequence homology with shellfish tropomyosin – with mites and cockroaches having 78.5–81.7% and 82.4% sequence identity to Pen a 1, a prawn tropomyosin [22,51]. It has been hypothesized that inhalant exposure to HDM tropomyosins is the primary sensitizer for shellfish allergies, with subsequent IgE cross-reactivity with shellfish tropomyosins accounting for the later age of onset and the predominance of oral symptoms observed in the Asia-Pacific region where HDMs are highly prevalent. These data are also supported by the high correlation between HDM sensitization and allergy, and shellfish sensitization in atopic populations [52,53]. IgE inhibition studies in a Spanish cohort with both HDM and shrimp allergies found almost complete inhibition of shrimp extract by a mite (*Chortoglyphus arcuatus*) on immunoblot inhibition studies, implicating HDM as the primary sensitizer [54].

Arginine kinase

Despite the central role of tropomyosin, other minor crustacean allergens remain clinically relevant. In a cohort of shrimp-allergic patients from Italy, 10–15% of patients were sensitized to arginine kinase and sarcoplasmic-binding protein, with only one case of cosensitization with tropomyosin, emphasizing the clinical importance of the minor allergens in some populations [55]. A cohort of

prawn-allergic patients from Singapore found a 21% sensitization rate to arginine kinase [35].

Arginine kinase is an essential enzyme in the regulation of cellular ATP levels [56]. It has been found in prawns, crayfish, crab and octopus [57–59]. Cross-reactivity between arginine kinase proteins belonging to different crab species has also been demonstrated in a Malaysian study of patients allergic to both red crab and blue crab [59].

Myosin light chain

Myosin light chain (MLC), a part of the myosin macromolecular complex in muscle protein, was first identified as an allergen in Pacific white leg shrimp (*L. vannamei*, Lit v 3) [60]. The frequency of allergic sensitization to MLC ranges between 19 and 55% [49,61].

Sarcoplasmic-binding protein

Sarcoplasmic binding proteins (SCBP), which bind calcium ions, have been identified as an allergen in tiger prawn *P. monodon* (Pen m 4) and Pacific white-leg shrimp *L. vannamei* (Lit v 4) [62,63]. In a cohort of Spanish shrimp-allergic patients, IgE recognition of SCBP was found to be higher in children than in adults, with greater sensitivity in predicting clinical reactivity to shrimp when analyzed in combination with tropomyosin-specific-IgE (sIgE) [56].

In comparison with tropomyosin, sensitization rates to the minor allergens are highly variable between shrimp allergic patients in different geographical regions and age groups, suggesting that the clinical importance of the minor allergens may vary significantly between different populations.

Other minor allergens: troponin, hemocyanin, triose phosphate isomerase, paramyosin

Troponin has been described as an allergen in tiger prawn, lobster and North sea shrimp, with IgE sensitization rates ranging from 12 to 29% [49,61]. Hemocyanin, a protein found mainly in the cephalothorax and hepatopancreas of prawns may be a potential cross-reactive allergen in crustaceans, dust mites, cockroaches and molluscs [64]. Triose phosphate isomerase has been characterized as a shrimp and octopus allergen [49,65]. Paramyosin has been identified as an allergen in molluscs such as abalone and pacific oyster [66,67].

DIAGNOSIS

The diagnosis of shellfish allergy is challenging due to the extensive repertoire of species and the high

degree of cross reactivity between the major allergen, tropomyosin, of different shellfish, as well as to house-dust mites and cockroach in sensitized individuals. As with other IgE mediated food allergies, a convincing clinical history and evaluation for sensitization with SPT and/or detection of serum-sIgE are essential. However, due to the poor correlation between cross-reactivity in SPT and clinical cross-reactivity, oral food challenges (OFCs) to individual shellfish species are often necessary for definitive diagnosis and appropriate management.

Skin prick tests with commercially prepared whole protein extracts are usually used as the first line investigation. Commercially prepared extracts have, however, shown significant variability in allergen content, species used (which may differ from major clinically relevant species in the population tested) and protein composition [68[†]]. In-house preparations or prick-prick tests with geographically relevant prawn species have been shown to have higher sensitivity than commercial SPT, albeit with low specificity [36,69].

Component resolved diagnostics and specific IgE to tropomyosin

Component resolved diagnostics (CRD) has increased the specificity of diagnosis in many food allergies. The use of prawn tropomyosin-sIgE has been shown to have a better positive predictive value for clinical reactivity, compared with SPT or whole extract sIgE [48,61]. However, there is still a significant (although smaller) percentage of patients who are mono-sensitized to minor allergens, with no concurrent sensitization to tropomyosin [55].

Allergen panels combining both major and minor species-specific allergens may be a promising approach to increase the accuracy of diagnosis. A panel of nine recombinant allergens from North Sea shrimp *Crangon crangon* was able to correctly identify 90% of shrimp allergic individuals analyzed [49]. Another study using a similar panel of allergens identified arginine kinase as having the highest sensitivity (48%) among the minor allergens [61]. However, despite the complete panel, the false negative rate was substantial – 12%. This finding was echoed in a cohort of Singaporean patients in whom 18% of prawn allergic patients had no evidence of sensitization to either whole protein extracts, tropomyosin or minor allergens [35]. These observations show that despite the promise of CRD, a diagnostic OFC is still required for accurate evaluation.

Sequential OFCs may be indicated if several shellfish species are to be investigated, to distinguish

between serological and clinical cross-reactivity; and avert unnecessary avoidance.

MANAGEMENT

At present, avoidance of the shellfish allergen is the only treatment available. Research on shellfish immunotherapy has focused on development of hypoallergenic variants of tropomyosin, through methods including enzyme cross-linking, polypeptide fragmentation and epitope manipulation [70,71]. Hypoallergenic shrimp tropomyosin mimotopes (peptides resembling epitopes of allergens which lack IgE cross-linking properties) have shown promising results in a murine model, but results remain at proof-of-concept stage in animal studies [72,73]. No clinical trials of shellfish immunotherapy have been reported so far. The intriguing mite-shellfish link suggests the possibility of innovative therapeutic approaches with immunotherapy for shellfish allergy, including the early use of HDM immunotherapy for primary prevention of shellfish allergy [74,75].

FURTHER DIRECTIONS FOR RESEARCH (CONCLUSION)

More studies with challenge-proven allergic subjects are needed to establish the true prevalence and natural history of shellfish allergy and to understand patterns of clinical cross-reactivity. There is a need for more reliable diagnostic tools to predict clinical reactivity as sIgE testing may be hampered by clinically insignificant serological cross-reactivity. Further work on uncovering novel species-specific allergens or components may allow more precise diagnosis of allergy to a specific species, eliminating the need for multiple OFCs.

Further investigations into the mechanisms and temporal relationship between HDM and shellfish sensitization will provide greater insight into the pathogenesis of the mite-shellfish oral allergy syndrome. The development of immunogenic hypoallergens and other innovative approaches will pave the way for novel immunotherapeutic strategies for shellfish allergy.

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Conflicts of interest

There are no conflicts of interest.

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