Shellfish allergy - an Asia-Pacific perspective

Alison Joanne Lee,[1] Irvin Gerez,[1] Lynette Pei-Chi Shek[1] and Bee Wah Lee[2]

Summary

Background and Objective: **Shellfish forms a common food source in the Asia-Pacific and is also growing in the West. This review aims to summarize the current literature on the epidemiology and research on shellfish allergy with particular focus on studies emerging from the Asia-Pacific region.**

Data Sources: **A PubMed search using search strategies "Shellfish AND Allergy", "Shellfish Allergy Asia", and "Shellfish AND anaphylaxis" was made. In all, 244 articles written in English were reviewed.**

Results: **Shellfish allergy in the Asia-Pacific ranks among the highest in the world and is the most common cause of food-induced anaphylaxis. Shellfish are classified into molluscs and arthropods. Of the arthropods, the crustaceans in particular Penaeid prawns are the most common cause of allergy and are therefore most extensively studied. Several classes of allergens have been identified. The tropomyosins (class 1 allergens) are the best defined. Despite the establishment of molecular homology and allergenic cross reactivity between allergens of the same class, clinical cross-reactivity is more variable between patients and less clearly defined. There are two relatively unique clinical manifestations of IgE-mediated prawn allergy: (1) isolated oral allergy symptoms; and (2) wide spectrum of severity and sometimes even within the same individual.**

Conclusion: **Shellfish allergy is common in the Asia Pacific. More research including food challenge-proven subjects are required to establish the true prevalence, as well as to understand clinical cross reactivity and variations in clinical features.** ***(Asian Pac J Allergy Immunol 2012;30:3-10)***

Key words: *Shellfish allergy, Prawn allergy, Shrimp allergy, Food allergy, Anaphylaxis, Tropomyosin, Allergens, Asia*

From the 1. Department of Paediatrics, University Children's Medical Institute, National University Health System, Singapore

2. Department of Paediatrics, National University of Singapore

Corresponding author: Bee Wah Lee

E-mail: lee_bee_wah@nus.edu.sg

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Introduction

Shellfish, which include crustaceans and molluscs, is one of the most common causes of food allergy in the world in both adults and children, and it has been demonstrated to be one of the top ranking causes of food allergy in children in the Asia-Pacific.[1-3] In addition, shellfish allergy usually persists, is one of the leading causes of food-induced anaphylaxis, and has been implicated as the most frequent food type to result in an emergency department consult in those aged above 6 years old.[4,5]

It has particular impact in the Asia-Pacific region where the consumption as well as the supply of seafood is the highest in the world. Shellfish comprises one quarter of this supply.[6] China and Japan are among the top three consumers (Northern America as second), with many other Asian countries such as India, Indonesia, Philippines, Korean Republic, Vietnam, Bangladesh and Thailand also listed among the top ten consumers of seafood worldwide.

This review aims to outline the epidemiology and highlight the major and clinically cross-reactive allergens in shellfish allergy, with particular focus on the Asia-Pacific region. A PubMed search strategy using the terms "Shellfish AND Allergy", "Shellfish Allergy Asia", and "Shellfish AND anaphylaxis" were performed. This search resulted in 285 articles. This review was limited to 'English' articles, resulting in 244 articles, of which 58 were review articles, and 29 were original articles from the Asia Pacific.

Classification of Shellfish

There is a perception amongst clinicians and lay persons that shellfish allergens are highly cross reactive and that clinical allergy to a particular shellfish would often necessitate avoidance of most shellfish. It is therefore worthwhile clarifying this notion as unnecessary avoidance may be advised. Clinicians managing shellfish allergy should also be conversant with the classification of edible shellfish, as well as the described allergens that are known to be cross reactive.

Edible seafood is classified into 3 main phyla – Mollusca, Arthropoda (crustaceans) and Chordata (fish). The term 'Shellfish' generally refers to the two invertebrate groups - the molluscs and crustaceans, which are further sub-categorised (Table 1). The chordata phylum includes finned fish, with the major class being Osteichthyes. However this group contains very different allergens from shellfish and will not be included in this review.[7]

Within the phylum crustaceans, 'prawns' and 'shrimps' are terms often used interchangeably. A 'shrimp' in the USA is known as a 'prawn' in Australia, and among some English-speaking regions in Asia. The modern day carcinologists (crustacean experts) also do not differentiate between these terms (personal communication P Ng, National University of Singapore). However, the generic use of 'prawns and shrimp' in medical literature is confusing because it may refer to species belonging to separate families within the taxonomy tree, and it is important to address these differences.[8]

Prawns and shrimps belong to the *Decapoda* ('10 footed' in Latin), which forms one of the largest crustacean groups (order of the malacostraca). This group also includes crabs, crayfish and lobsters. *Decapoda* almost always have 5 pairs of legs on the main thoracic body and 5 pairs of swimmerets on the abdomen or tail. Within the class *Decapoda*, the commonly used terms, 'prawns and/or shrimps' usually refer to the group, *Penaeidae*. However, there exists another *Decapoda* family, the *Caridea*, which are also referred to as 'shrimp', and it is important to establish that *Penaeidae* and *Caridea* are different and belong to separate taxonomical crustacean families. Penaeids are *usually* larger and of greater commercial impact, and are the most commonly implicated food in shellfish allergy. Hence, in this review, the term 'prawn' will refer to the Penaeids and the term 'shrimp' refers to a different group, Carideans.

Table 1. Classification of Shellfish, Fish and Arthropod species

Common reference	Phyla	Subphyla	Class	Common Name
"Shellfish" (inverte-brates)	Mollusca		Gastropoda	Abalone, snails (escargot), welk
			Bivalvia	Mussels, oysters, clams, scallop, cockle
			Cephalopoda	Squids (calamari), octopus, cuttlefish
	Arthropoda	Crustacea	Malacostraca	Shrimps (caridea), prawns (penaeidae), crabs, lobsters, crayfish
	Arthropoda	Chelicerates	Arachnida	Spiders, mites (including house dust mites)
			Xiphosura	Horseshoe crab
		Hexapoda	Insecta	Cockroaches, wasps, bees, butterflies
		Myriapoda		Centipedes, millipedes
"Fish"	Chordata		Osteichthyes (main class)	Salmon, tuna, cod, grouper, snapper, tuna

Anatomically, the Penaeid prawns and Caridean shrimps differ in the way the segments overlap, leg proportions and how they brood their eggs.[8] The Caridean shrimps are often inedible due to their small size, but could come commercially packed in cans or preserved-dry packets, which are used for food flavouring in Asian cooking. There are however, exceptions, and Caridean shrimps may also be large in size. For example, freshwater Caridean shrimp (*Macrobrachium Rosenbergii*) are quite large and can grow to over 30cm in length. This freshwater Caridean shrimp is frequently eaten and popular as a food in South East Asia. Of interest are the recent reports of mono-allergy to freshwater shrimps, *Macrobrachium Rosenbergii* and *Macrobrachium Lanchesteri*, in the Thai population, without concomitant prawn allergy.[9,10]

There are several thousand species of prawns and shrimp. The most common prawns eaten in Singapore and Asia are the black tiger prawns (*Penaeus monodon)*, the white leg pacific prawn

Table 2. Shellfish Allergens and Allergen Nomenclature[#]

	Tropomysin	Arginine Kinase	Myosin Light Challenge	Sarcoplasmic calcium-binding protein	Others
Crustaceans					
Prawn, Black tiger (Penaeus monodon)	Pen m 1	Pen m 2		Pen m 4	
Prawn, Brown (Penaeus aztecus)	Pen a 1				
Prawn, White leg pacific (Litopenaeus vannamei)	Lit v 1	Lit v 2	Lit v 3		
Prawn, Fleshy (Fenneropanaeus chinensis)	Fen c 1	Fen c 2			
Prawn, Tiger (Marsupenaeus japonicus)	Mar j 1	Mar j 2		Mar j 4	
Prawn, Banana (Fenneropenaeus merguiensis)	Fen me 1				
Prawn, fleshy (Penaeus orientalis)	Pena o 1				
Prawn, sand (Metapenaeus ensis)	Met e 1				
Shrimp, Giant fresh water (machrobrachium rosenbergii)	Mac ro 1				Mac ro hemocyanin
Crab, Mud (Scylla paramamosain)	Scy pa 1	Scy pa 2			
Crab, Snow (Chionoecetes opilio)	Chi o 1	Chi o 2		Chi o 4	
Krill, Antartic (Euphasia superba)	Eup s 1				
Krill, Pacific (Euphasia pacifica)	Eup p 1				
Lobster, American (Homarus americanus)	Hom a 1		Hom a 3		
Lobeter, Rock (Jasus Lalandii)	Jas la 1				
Lobster, Spiny (Panulirus stimpsoni)	Pan s 1				
Molluscs					
Abalone (Haliotis discus)	Hal d 1				
Abalone (Haliotis midae)	Hal m 2				
Abalone (Haliotis rufescens)	Hal r 1				
Common whelk (Buccinum undatum)	Buc u 1				
Mussel, Tropical Green (Perna viridis)	Per v 1				
Octopus, Common (Octopus vulgaris)	Oct v 1				
Oyster, Pacific (Crassostrea gigas)	Cra g 1				
Clam, Razor (Ensis macha)	Ens m 1				
Cockles, Japanese (Venerupis philippinarum)	Ven ph 1				
Scallop, Japanese (Chlamys Chlamys nipponensis)	Chl n 1				
Scallop, Giant (Patinopecten yesooensis)	Pat y 1				

Allergen nomenclature obtained from Allergome database (http://www.allergome.com)

(*Litopenaeus vannamei*), the white or banana prawn (*Fenneropenaeus merguiensis*), green tiger prawn (*Penaeus semisulcatus*), and Angka or cold water shrimp (*Pandalus borealis*) which is imported from colder climes.

Shellfish Allergens

Molecular allergology has facilitated the identification of individual allergens of shellfish. There are four groups of crustacean allergens that have been identified and cloned. These are Group 1: tropomyosin, Group 2: arginine kinase (AK), Group 3: myosin light chain (MLC), and Group 4: sarcoplasmic calcium-binding protein (SCP). These crustacean allergens are listed in Table 2 according to their common and biological names.

Of the allergens identified, Group 1 tropomyosin, which is 34 to 36kDa, is considered a major allergen for prawn, and other crustaceans, such as shrimp, crayfish, lobster, crab and barnacles. Tropomyosin is found in the muscular tissue of both vertebrates and invertebrates and is considered a pan-allergen (see section on cross reactivity). Group 2 allergens, arginine kinase, are 40-kDa minor allerge identified in the black tiger prawn (Pen m 2), and white leg pacific prawn (Lit v 2).[11,12] More recently, Ayuso et al. demonstrated IgE binding to a 20-kDa protein from the white pacific prawn (*Litopenaeus vannamei*), Lit v 3, which was further identified as a myosin light chain (MLC); and Lit v 4, sarcoplasmic calcium-binding protein.[13-15]

Allergenic Cross reactivity

Shellfish allergens

Cross-reactivity of phylogenetically related species across the molluscan and crustacean phyla is well established. There is high molecular (amino acid) homology between the tropomyosin allergens of phylogenetically related crustacean species of up to 98%. For molluscan shellfish, a similar intra-class amino acid similarity exists for tropomyosin allergens for gastropods, cephalopods and bivalve groups of 85 to 97%, 91 to 100% and 70 to 100% respectively. Additionally, the homology across the molluscan classes (that is between gastropods, cephalopods and bivalves) are similar and ranges between 68 to 100%.[16] The degree of homology between crustacean and mollusca tropomyosin sequence identity is much lower, 56 to 68%. For example, the homology between Tod p 1, which is a cross-phylum specific allergen in squid (*Todarodes pacficus)* is about 62% homologous to regional prawns (*Penaeus orientalis* and *Metapenaeus ensis*).[16]

This molecular homology of shellfish tropomyosins translates to high degrees of IgE cross reactivity. Several studies have reported high rates (up to 90%) of IgE cross-reactivity between crustaceans and the mollusca group based on skin prick testing.[17,18] Clinical cross reactivity, however, does not appear to correlate as closely. Sicherer et al. showed in a USA telephone survey on self-reported shellfish allergy that only 38% were allergic to more than 1 crustacean species, and likewise only 49% were allergic to more than 1 molluscan species. Additionally, the authors also reported that only 14% of the shellfish allergic US population reported both crustacean and mollusc hypersensitivity. Recent studies on food challenges in Thai prawn allergic subjects refutes the notion that shellfish pan allergy is a rule. The authors showed by food challenges that a proportion would react to a black tiger prawns (*penaeus monodon*) but not to the fresh water Caridean shrimp, *Macrobrachium Rosenbergii* and vice.[9] Furthermore, Piboonpocanun et al. recently identified hemocyanin as a novel non-cross-reactive allergen of the giant freshwater shrimp, *Macrobrachium rosenbergii*.[19]

Hence, IgE cross-reactivity may not translate to overt clinical allergy, and more studies with food challenge proven clinical outcomes are necessary to identify rates of cross-reactivity between crustaceans and molluscs. The perception that all patients with crustacean allergy should avoid all other crustaceans and molluscs including squid, abalone, scallops, mussels, clams and oysters, may not be accurate. Individualized management would be ideal, but this would likely entail food challenge testing.

Arthropod allergens

Shellfish are phylogenetically related to insects and arachnids and are classified under the same phylum *Arthropoda*, which are invertebrates with an exoskeleton, segmented body and jointed appendages (Table 1). Of interest and possible clinical significance is the cross reactivity of shellfish allergens across phylogenetically related species such as the insects (cockroach) and arachnids (dust mites). Of these allergens, tropomyosin has been the most studied and described, and has been considered a pan allergen.[20] There is 81% amino acid sequence similarity of the tropomysin between prawns and mites, and 82% between prawns and cockroach, which is even higher than that between shellfish and molluscs. Furthermore, specific IgE-binding epitopes of the brown prawn (Penaeus aztecus) tropomysin allergen Pen a 1 has up to 100% homology with similar epitopes of the house dust mite (*Dermatophagoides pteronyssinus, D. farinae and Blomia tropicalis*) tropomysins (Der p 10, Der f 10 and Blo t 10), and the American cockroach *(Periplaneta Americana*) tropomysin (Per a 7).[21,22]

The clinical significance of this cross reactivity has been suggested by several studies. These studies include data in an orthodox Jewish community who abstain from shellfish according to kosher law. Dust mite and cockroach sensitized individuals from this community, also displayed sensitization to shellfish suggesting cross reactivity between tropomyosins.[23] Furthermore, in a study of 17 house dust mite allergic patients receiving immunotherapy, three patients developed IgE against Caridean shrimp. Two subjects with IgE against shrimp and mite tropomyosin had oral allergy symptoms after ingesting shrimp.[24] These data suggests that primary sensitization to dust mite

Table 3. Global Prevalence of Shellfish Allergy

Region	Age (years)	n	Self-report only	Self-reported and IgE-sensitization	Confirmed by Oral food challenge	Reference
Philippines	14-16	11158	*5.12			Shek, et al[27]
Singapore	14-16	6342	*5.23			Shek, et al[27]
	4-6	4115	*1.19			
Hong Kong	2-7	3677	1.28			Leung, et al[30]
China, Chongqing	< 1	477	0.2	0.2		Chen, et al[44]
Australia	< 1	2848		0.40		Osborne, et al[45]
Canada	All ages	9667	*1.42	0.73		Ben-Shoshan, et al[41]
	Children^		0.50	0.06		
	Adults^		1.70	0.70		
Denmark	Overall	1834	0.60		0.16	Osterballe, et al[32]
	0.1 - 22	898	0.1		0	
	22-60	936	1.1		0.30	
France	2-14	2716	1.4			Rance et al[33]
USA	18-61	9816	*2.60			Sicherer et al[26]
	Overall	14948	*2.00			
	0-18	2707	*0.70			

^Exact ages not specified, *Based on reliable history of IgE-mediated food allergy

and cockroach tropomyosin may result in clinical shellfish allergy and would require population studies to verify.

Epidemiology

Table 3 summarizes the published studies on the prevalence of shellfish allergy. The overall prevalence of shellfish allergy in the western world (USA, Canada and Europe) is about 0.6%, ranging between 0 to 10%.[25] Of the shellfish, prawns are most frequently implicated (62% of shellfish allergy), followed by crab, lobster and then the molluscan species.[26] In Asia, a similar pattern of shellfish allergy is seen.[27] Although most of the prevalence studies did not include concurrent IgE sensitization and food challenges, the prevalence in Asian populations is likely to be more common than the western world as discussed below. This is in stark contrast to peanut and tree nut allergy in children, where the focus of this 'epidemic' is in the west.[28]

Based on a questionnaire survey in schoolchildren in Singapore and the Philippines, the self-reported symptoms of convincing shellfish allergy was 1.19% in 4 to 6 year olds (Singapore only) and more than 5% in 14 to 16 year olds (Singapore and Philippines). Similar findings of relatively high shellfish allergy prevalence rates among Asian children were demonstrated in Hong Kong at 1.3% (2 to 7 years old). Shellfish also ranks among the top most common causes of food allergy in Asian countries such as Thailand, Japan, and Taiwan.[3,10,29,30] In western populations self-reported rates of shellfish allergy are significantly lower at 0.7% in children less than 16 years old in USA, 0.1% in less than 22 year olds in Denmark, 1.4% in 2 to 14 year olds in France, and rare in 6 year olds in the United Kingdom.[26,31-33] Furthermore, cow's milk, hen's egg, peanut, tree nuts and fruits tend to rank above shellfish allergy in children in these western populations.[4,31,34]

The notion that the prevalence of shellfish allergy is higher in the east compared to the west is further substantiated by the lower prevalence of reported shellfish allergy among expatriates living in Singapore compared with the local population, suggesting differences in culture and background may influence the rates of shellfish allergy.[27]

Clinical Manifestations

The clinical features of IgE-mediated shellfish allergy vary widely in severity from mild oral symptoms to life threatening anaphylaxis. Unlike other well described food allergies such as peanut, cow's milk and egg allergy, a common manifestation of shellfish allergy are mild oral symptoms confined to the lips and oral mucosa.[9] These symptoms are reminiscent of the oral allergy (pollen-food) syndrome described by subjects with pollen allergy consuming fruits and nuts. It has been hypothesized that inhalation of dust mite or cockroach allergens, which are ubiquitous in the tropics, may be the primary sensitizer in individuals with isolated oral symptoms due to shellfish allergy, but this is not established in population studies.

Another interesting phenomenon regarding the clinical manifestation of prawn allergy is the varying severity of reaction within the same individual (unpublished data). It is not uncommon for patients who have reacted to prawns to continue eating it on different occasions, as oftentimes the symptoms are mild and tolerated. Some of these individuals, however, may develop a severe life threatening reaction occasionally. The variability may be explained at least in part by 2 possibilities: differences in allergenicity of species of prawns/shrimp consumed; or variation in the part of the prawn consumed. The most commonly eaten part of the prawn is the abdomen. In Asian and some European countries, the cephalothorax ('the head'), comprising the brain, heart, stomach and bladder) is also widely eaten. Interestingly, a study by Rosa et al. highlighted 3 cases where there was clinical reaction only to the cephalothorax of the prawn.[35] Each patient demonstrated a positive skin prick test to prawn cephalothorax and a negative skin prick test to prawn abdomen. They were further challenged to prawn abdomen without any allergic symptoms. The study also showed that different allergens exist in the prawn abdomen and prawn cephalothorax, which may account for the difference.

In adults and older children, it is well established that shellfish is also the most frequently implicated food causing anaphylaxis as evidenced by presentation to emergency departments in the studies from the USA, Singapore, Hongkong and Thailand.[36-39] In younger children less than 6 years old, shellfish is less frequently implicated but still ranks among the top 5 foods in some studies.[5,40]

There are few published studies on the natural history of shellfish allergy, and none of these were from Asia. Shellfish allergy more frequently starts in adulthood, however even those which start at an early age have persistent allergy. A study from Canada by Ben-Shoshan et al. showed that the median age of onset of shellfish allergy was 25 years in a group of 122 adult shellfish allergic participants with a reliable history of shellfish allergy.[41] In the group of children, the median age was 6.5 years.[41] Daul et al. showed that prawn-specific IgE levels remained constant over a 24 month period suggesting persistence of allergy.[42] In contrast, a recent cross sectional study by Ayuso et al. demonstrated higher levels of shrimp-specific IgE and more intense IgE allergen binding in shrimp allergic children compared to adults. The authors suggested that allergen sensitization may decrease with age and that in some the allergy may not be long term.[43]

In conclusion, shellfish allergy among adults and children in the Asia-pacific is fairly prevalent and ranks as one of the most common foods causing allergy. The clinical manifestations are varied, sometimes even in the same subject. There is evidence of cross-reactivity between different species, but this does not always correlate with clinical cross-reactivity. With this in mind, more studies incorporating challenge-proven subjects focusing on understanding clinical cross-reactivity are necessary to better understand, and hopefully manage, shellfish allergy in this region.

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