

Contemporary Issues in Food Allergy: Seafood Toxin-Induced Disease in the Differential Diagnosis of Allergic Reactions

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ABSTRACT

Seafood, including fish, shrimp, lobster, crab, crayfish, mussel, and clam are among the most frequent causes of food allergy. Seafood poisoning, including reactions to natural toxins, frequently masquerades as an allergic reaction on presentation. Ingestion of contaminated shellfish results in a wide variety of symptoms, depending on the toxins present, their concentrations in the shellfish, and the amount of contaminated shellfish consumed. Five types of shellfish poisoning have been identified clearly including paralytic, neurotoxic, diarrhetic, amnesic, and azaspiracid shellfish poisonings. Based on the presence or absence of the toxin at the time of capture, fish poisoning can be considered conceptually in two categories. In ciguatera and puffer fish poisoning, the toxin is present in live fish, whereas in scombroid, it is produced only after capture, in the fish flesh, by contaminating bacteria because of improper refrigeration. Most shellfish-associated illness is infectious in nature (bacterial or viral), with the

Norwalk virus accounting for most cases of gastroenteritis. (Allergy and Asthma Proc 26:183–190, 2005)

INTOXICATIONS ASSOCIATED WITH FISH

Scombroid (Histamine Poisoning)

Scombroid poisoning is characterized by a constellation of gastrointestinal (GI), neurological, cardiovascular, and cutaneous symptoms (Table I). In severe cases and in persons with asthma, bronchospasm may develop. The most frequent symptoms are tingling and burning sensations around the mouth, GI complaints, and a skin rash. Patients sometimes describe a peppery or bitter taste to the fish. The onset of symptoms usually is within 10–30 minutes of ingesting the fish. Physical signs may include a diffuse blanching erythema, tachycardia, wheezing, and hypotension or hypertension. Immediate reactions may be indistinguishable from anaphylaxis and scombroid often is misdiagnosed as an allergic reaction.¹

Scombroid intoxication results from ingestion of fish containing high levels of free histamine (Table II). Because histamine is resistant to heat, cooking the fish and even high temperatures used in the canning process will not prevent scombroid poisoning. Because the symptoms usually are self-limited and resolve in the vast majority of cases within 4–10 hours without any sequelae, often, there is no need for specific treatment. However, H1 and H2 antihistamines ameliorate the symptoms in severe cases.²

The histamine is not present when the fish are caught but is later produced during spoilage by decarboxylation of free histidine, which is naturally present at high levels in species of fish implicated in scombroid. The production of histamine is caused by the action of histidine decarboxylase, an

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TABLE I

Seafood-Associated Disease in the Differential Diagnosis of Allergic Reactions

- A. Common seafood poisons
 1. Fish poisoning
 - a. Ciguatera
 - b. Scombroid
 - c. Tetrodon poisoning
 2. Shellfish poisoning
 - a. Paralytic
 - b. Neurotoxic
 - c. Amnesic
 - d. Diarrheic
- B. Less common seafood poisoning
 1. Fish
 - a. Clupeotoxin
 - b. Elasmobranch
 2. Mollusks
 - a. Red whelks
- C. Infections and bacterial intoxications
 1. Bacterial toxins
 - a. *Clostridium botulinum*
 - b. *Staphylococcus aureus*
 2. Bacterial infections
 - a. *Vibrio cholerae*
 - b. *Vibrio parahaemolyticus*
 - c. *Vibrio vulnificus*
 3. Viral infections
 - a. Norwalk and Norwalk-like enteric viruses

enzyme produced by bacteria such as *Morganella morganii*, *Klebsiella pneumoniae*, and *Hafnia alvei*. Laboratory confirmation of scombroid is based on showing elevated histamine levels >50 ppm in the muscle tissue of incriminated fish.³

Ciguatera

Ciguatera fish poisoning is a clinical syndrome that presents after consumption of ciguateric fish with characteristic GI, neurological, and, occasionally, cardiovascular symptoms. The onset of the symptoms varies between 10 minutes and 12 hours after ingestion of contaminated fish. Nausea, vomiting, watery diarrhea, and abdominal pain usually develop within 3–6 hours and typically last 12–24 hours. Neurological symptoms include paresthesias that initially involve the lips, tongue, and throat, which later may extend to the extremities, hypoaesthesia, dysesthesias, pruritus, generalized weakness, anxiety, and reversal of temperature sensation.⁴ Other less common symptoms include diaphoresis, chills, dizziness, headache, blurred vision, prostration, myalgias, dry mouth, taste disturbances or a metallic taste, and pain or a loose sensation in the teeth. Mean duration of acute illness typically is 8.5 days, although it is not unusual for neurological symptoms such as paresthesias or temperature reversal to

periodically reoccur for a month or longer. Cardiovascular symptoms are found in 10–15% of cases and, when present, bradycardia or hypotension may require urgent management. In cases of severe intoxication, seizures, coma, and respiratory paralysis may occur, which in the absence of adequate life support can be fatal.⁵

Ciguatoxins (CTXs), the toxins responsible for ciguatera are produced by *Gambierdiscus toxicus*, a marine dinoflagellate that belongs to the family of benthic macroalgae. They are lipid-soluble, polyether toxins that, when ingested by certain subtropical and tropical finfish, can accumulate in their tissues. CTXs activate voltage-dependent sodium channels, causing cell membrane excitability and instability. *In vitro* studies suggest that the CTX causes a nerve conduction block after initial neural stimulation.⁶

Maitotoxin is a water-soluble polyether phytotoxin also produced by *G. toxicus* that is distinct from CTX. It is a potent activator of a voltage-independent, nonselective cationic channel that results in elevation of the intracellular Ca^{2+} concentration, which ultimately is responsible for its toxicity.⁷

CTX are heat stable; therefore, they are not inactivated by either cooking or freezing. They are not affected by gastric acid and are harmless to the fish itself. Because they are odorless, colorless, and tasteless, ciguateric fish look, taste, and smell normal, and detection of toxins in fish remains a problem. Because there is no approved assay for CTX in humans, the diagnosis is based on clinical findings and by the detection of toxin in samples of fish. Any uneaten portions of fish should be saved in a freezer and submitted to state or local public health officials when suspected cases are reported to assist with the investigation and control of a possible outbreak.⁸ There is no immunity and no known antidote for CTX poisoning. Treatment is primarily supportive and for relief of symptoms.

Puffer Fish (Tetrodon) Poisoning

Symptoms begin with paresthesias 10–45 minutes after ingestion, and usually a stinging of the lips, tongue, and inner surface of the mouth. Common symptoms include headache, lightheadedness, dizziness, vomiting, diaphoresis, pallor, weakness, malaise, and feelings of doom.⁹ Some patients may experience a floating sensation, salivation, muscle twitching, and pleuritic chest pain. Depending on the amount of tetrodotoxin (TTX) ingested, the patient may experience ataxia, dysphagia, aphonia, and convulsions. Severe poisoning is indicated by hypotension, bradycardia, depressed corneal reflexes, and fixed dilated pupils. An ascending paralysis develops, and death can occur within 6–24 hours, secondary to respiratory muscle paralysis. Prognosis is good if the patient survives the first 24 hours.

Diagnosis is based on clinical symptoms and a history of recent consumption of suspect fish. Treatment is supportive, including active airway management and ventilatory and circulatory support as needed. To minimize the amount of

TABLE II

Syndromes Associated with Naturally Occurring Toxins in Seafood

Type of Poisoning	Type of Toxin	Source	Symptom Onset	Clinical Syndrome
Scombroid	Histamine	Tuna, mahi mahi, bonita, marlin, bluefish, wahoo, mackerel, and Salmon	Minutes to 4 hours	Severe headache, dizziness, nausea, vomiting, flushed skin, urticaria, and wheezing
Ciguatera	CTX, Maitotoxin	Coral reef fish: amberjack, snappers, grouper, goat fish, barracuda, sea bass, surgeon fish, ulua, and papio	1–4 hours	Abdominal pain, diarrhea, vomiting, paresthesias, cold-to-hot sensory reversal, weakness, and myalgias
Puffer fish	TTX	Ocean sunfishes, porcupine fishes, and fugu	10–45 minutes	Paresthesias headache, vomiting, diaphoresis, and respiratory paralysis
Paralytic shellfish	STX	Mussels, clams, and oysters	5–30 minutes	Vomiting, diarrhea, facial paresthesias, and respiratory paralysis
Neurotoxic shellfish	Brevetoxins	Mussels and clams	30 minutes–3 hours	Diarrhea, vomiting, abdominal pain, myalgias, paresthesias, and ataxia
Amnesic shellfish	DA	Mussels, clams, crabs, and anchovies	15 minutes–38 hours	Vomiting, diarrhea, headache, myoclonus, loss of short-term memory, seizures, coma, and hemiparesis
Diarrheic shellfish	Okadaic acid, Dinophysistoxins, Pectenotoxins, Yessotoxin	Mussels, clams, and scallops	30 minutes–6 hours	Diarrhea, nausea, vomiting, and abdominal pain

toxin absorbed, gastric lavage and activated charcoal may be beneficial soon after the ingestion. There is no specific antitoxin for human use.

Puffer fish poisoning is rare in the United States. It follows ingestion of certain species of fish belonging to the order Tetraodontidae that includes ocean sunfishes, porcupine fishes, and fugu.¹⁰ These fish characteristically inflate to several times their normal size by swallowing air or water when feeling threatened. The liver, gonads, intestines, and skin of these fish contain TTX but the flesh is edible if cleaned and prepared properly and is considered a delicacy. All puffer species in the U.S. waters, including *Sphoeroides maculatus*, *Sphoeroides annulatus*, and *Arothron hispidus* have been implicated in fatalities.

TTX is a heat-stable alkaloid that blocks sodium conductance and neuronal transmission in skeletal muscle. The natural source of TTX was identified in marine *Vibrio* species that are part of puffer fish microflora rather than the fish itself that merely accumulates the toxin in its tissue.¹¹ It is interesting that TTX also is present in other species such

as blue-ringed octopus, as well as some newts and toads.^{12,13} For the very toxic fish, consumption of as little as 10 g of the toxic tissue may be fatal and 1–4 mg of TTX constitutes a lethal dose for humans.

INTOXICATIONS ASSOCIATED WITH SHELLFISH

Paralytic Shellfish Poisoning

Paralytic shellfish poisoning (PSP), which is caused by saxitoxins (STXs), is the best known of the shellfish poisonings and causes the most severe symptoms. It is a serious illness in which neurological symptoms predominate. The first and most consistent symptom is numbness, tingling, or burning of the lips, tongue, and throat that begin within 30 minutes of ingestion. Paresthesias spread to the face and neck and often to the fingertips and toes. They always precede muscular weakness that affects the upper and lower limbs and in more severe cases are followed by dysphonia, dysphagia, and ataxia. Paralysis may occur

within 2–12 hours, which may persist for as long as 72 hours. Diaphoresis, nausea, vomiting, diarrhea, tachycardia, and temporary blindness may occur also. Reflexes may be normal or absent, and most patients remain calm and conscious throughout. Death can result from paralysis of the respiratory muscles within 2–24 hours, depending on the dose. Prognosis is good for individuals surviving past 12 hours. The duration of the illness may be from a few hours to a few days but occasionally muscular weakness can persist for weeks after recovery. Diagnosis is based on characteristic symptoms and on a history of recent ingestion of shellfish. However, examination of water samples for toxic algae and laboratory tests on the suspect food can provide supportive evidence.

Treatment is symptomatic. Gastric emptying has been advocated by some authors as an early treatment and activated charcoal generally has been recommended to help block further absorption of the toxins. Airway management and ventilatory support is the mainstay of treatment and can be lifesaving. Fluid therapy facilitates renal excretion of the toxin.

In the United States, PSP is a problem primarily in the New England states on the East Coast and in Alaska, California, and Washington on the West Coast. Most disease incidents involve mussels and clams gathered and eaten by recreational collectors. Bivalve mollusks such as mussels, clams, and oysters assimilate and temporarily store STX, a complex of neurotoxins produced by dinoflagellates. They are among the most potent neurotoxins known. The positively charged guanidinium group of the toxins binds specifically to a negatively charged site of the sodium (Na^+) channel on the extracellular side of the plasma membrane of nerve and muscle cells, thus blocking the flow of Na^+ through the channel. There is great variation in individual susceptibility and children are thought to be more susceptible. As little as 120–180 μg of STX can induce moderate symptoms in adults, and fatalities have been associated with levels of 0.3–12 mg. Although normal steaming or boiling will not inactivate the toxins, exposure of toxic shellfish to high temperatures (e.g., in the sterilization step of the canning process) substantially reduces STX concentrations.¹⁴ The mouse bioassay has been the classic method for analysis of STX.

The best way to prevent PSP is to adhere to the public health agency guidelines on harvesting, processing, and consumption of shellfish. To further minimize the risk of PSP, the public should avoid collecting shellfish from areas of known red tides and refrain from consuming suspect shellfish. In addition, because the toxins are water soluble, they can dissolve and concentrate in the broth, which should be discarded after cooking or steaming.

Neurotoxic Shellfish Poisoning

Neurotoxic shellfish poisoning (NSP) is characterized by both GI and neurological symptoms. The illness resembles a mild case of ciguatera or PSP but without a

paralytic component. The onset is rapid and symptoms occur within 3 hours after the ingestion of contaminated shellfish. Symptoms include numbness of lips, tongue, and throat; paresthesias, initially circumoral, which then spread to other parts of the body; reversal of hot and cold temperature sensation; muscular aches; dizziness; nausea; vomiting; diarrhea; abdominal pain; and headache. The intoxication usually is self-limited and resolves spontaneously within a few hours. Treatment is supportive and generally all patients recover with no after effects within a few days. There are no known antidotes for the toxin.

Interestingly, unlike other shellfish toxins, the brevetoxins can aerosolize by surf and wave action along the beach during red tides. Irritant toxin aerosols produce a syndrome characterized by conjunctival irritation, sneezing, and rhinorrhea that resembles an allergic response. Also, they trigger shortness of breath, nonproductive cough, and wheezing due to bronchospasm in individuals with underlying asthma or chronic obstructive pulmonary disease that can precipitate severe respiratory distress. The syndrome is self-limited and treatment of the bronchospastic episodes due exposure to aerosolized toxins is symptomatic. In 1987 during a red tide off the coast of North Carolina,¹⁵ 48 cases were reported that experienced upper and/or lower respiratory symptoms.

Karenia brevis (formerly *Gymnodinium breve*) is the dinoflagellate that synthesizes BTX, a group of related, heat-stable toxins that are responsible for clinical manifestations of NSP. BTXs are lipid-soluble polyether toxins of unique structure and pharmacologic function. Filter-feeding bivalve mollusks, such as oysters, clams, and mussels that consume *K. brevis* concentrate the toxins in various organs and become toxic to humans but remain unaffected. NSP in the United States generally is associated with the consumption of shellfish harvested along the coast of the Gulf of Mexico from Florida to Texas, and, sporadically, along the southern Atlantic coast. This is identical with the geographic distribution of *K. Brevis* blooms also known as “red tides” because a red coloration of seawater is observed easily.

Amnesic Shellfish Poisoning

Amnesic shellfish poisoning (ASP) presents initially with vomiting, diarrhea, and abdominal cramping within 24 hours after ingestion of contaminated shellfish. In some cases, varying degrees of neurological dysfunction ensues within 48 hours, including confusion, loss of memory, and disorientation. Other neurological symptoms are headache, hyporeflexia, hemiparesis, ophthalmoplegia, and abnormalities of arousal ranging from agitation to coma, seizures, and myoclonus, especially affecting the face. Loss of short-term memory is unique among the marine poisonings, hence, the name ASP. It is the most persistent symptom and can be permanent.

The syndrome was first described in a series of outbreaks in persons that had eaten mussels cultivated in the river

estuaries of Prince Edward Island in Canada from November through December 1987.¹⁶ In this cohort, 25% experienced loss of short-term memory. Nineteen patients (18%) were hospitalized, of whom 12 required intensive care because of seizures, coma, profuse respiratory secretions, or unstable blood pressure. Severity of the disease and permanent neurological sequelae, especially cognitive dysfunction, are associated with age over 60 years, male sex, and preexisting illnesses, as well as the amount of mussels consumed. Three elderly patients died directly and one died indirectly from the intoxication.

In mussels left uneaten by the patients, as well as mussels harvested later from the same estuaries, the toxic agent was isolated and identified as domoic acid (DA). Its concentration ranged from 31 to 128 mg/100 g of mussel meat, which suggested an estimated ingestion of 60–290 mg of DA per patient. The source of DA in Prince Edward Island in 1987 subsequently was identified as the phytoplanktonic diatom *Pseudonitzschia multiseries*, formerly known as *Nitzschia pungens*.¹⁷ ASP is the only shellfish poisoning caused by diatoms. DA is a potent neurotoxin that accumulates in mussels and clams that feed on toxic plankton during their bloom.

Diagnosis is based on a recent history of shellfish ingestion and is made on clinical grounds. It is confirmed by the presentation of DA in shellfish samples. At this point, the treatment of ASP is symptomatic and supportive. Seizures respond well to parenteral benzodiazepines and phenobarbital. There is no antidote and immunity does not develop.

Diarrhetic Shellfish Poisoning

Diarrhetic shellfish poisoning (DSP) is the mildest and most benign of the toxic shellfish poisonings. Clinical features generally are limited to the GI tract and include diarrhea, nausea, vomiting, abdominal pain, and cramps. Chills, fever, or headache also may be present in up to 10% of cases. The symptoms usually manifest in a period ranging from 30 minutes to 6 hours after ingestion of contaminated shellfish and persist on the average for 36 hours. No known fatalities have occurred, and total recovery is expected within 3 days. Because of the transient nature of the illness and its spontaneous resolution, often patients do not seek medical attention; however, the duration could be shortened with charcoal, which reduces the bioavailability of the toxins and its repeated administration interrupts their enterohepatic recirculation. Treatment, if required, is limited to alleviation of symptoms.

DSP is associated with the consumption of mussels, scallops, clams, and oysters contaminated with biotoxins produced by toxic marine dinoflagellates during their blooms in the summer. At present, for the U.S. consumer, the risk of DSP is limited to imported products and should be controllable by import regulations that permit import of shellfish only from countries that test it for the presence of toxins.

LESS COMMON SEAFOOD POISONINGS

Clupeotoxism, is a highly fatal form of human intoxication caused by ingestion of clupeidae (herring-like fish). It is a rare poisoning occurring in the tropics only during the warm summer months. Like ciguatera, it occurs sporadically and over an extensive area of the tropical Pacific and Indian Ocean coasts. Symptoms include nausea, vomiting, diarrhea, abdominal pain, headache, dry mouth, sweats, chills, lightheadedness, and paresthesias and in one report, one of two patients with clupeotoxism died.¹⁸ The causative toxin is palytoxin, one of the most potent phyco-toxins known so far. The benthic dinoflagellate *Ostreopsis siamensis* has been identified as the source of palytoxin.¹⁹ Plankton feeders such as herring, pilchard, tarpon, and anchovies that ingest it can become toxic.

Elasmobranch poisoning is caused by the ingestion of contaminated meat or liver from several species of sharks, most notably the Greenland sleeper shark. The disease is characterized by GI and neurological symptoms including nausea, vomiting, diarrhea, abdominal pain, headache, and perioral paresthesia. Severe progressive respiratory distress, hyporeflexia, and coma usually precede death. The onset of symptoms is 30 minutes to 5 hours after ingestion. Carcha-toxin-A and -B, two novel lipid-soluble toxins were isolated from the shark's liver, which were distinct from other known marine toxins.²⁰

In red whelk poisoning, symptoms develop within 30–120 minutes, which include headache, dizziness, blurred vision, or diplopia, paraesthesias, dry mouth, muscular twitching or cramps, ataxia, weakness, and collapse. Nausea, vomiting, and diarrhea also may be present in some patients. The red whelk (*Neptunea antiqua*) is a gastropod species common in Japan and North European waters. It contains a heat-stable toxin tetramine, which is present in the salivary gland, and produces symptoms because of its curare-like effect. Because symptoms resolve rapidly and recovery is complete within 24 hours, few people are likely to seek medical attention.

POISONING DUE TO BACTERIAL TOXINS

Botulism

Food-borne botulism is acquired from ingestion of food contaminated with preformed toxin that is produced by *Clostridium botulinum*, a sporulating, anaerobic Gram-positive bacillus. It is characterized by symmetric, descending, flaccid paralysis of motor and autonomic nerves, usually beginning with the cranial nerves, which may be fatal because of respiratory failure. Onset is abrupt, usually 12–36 hours after ingestion of toxin. The first manifestations often are dry mouth, diplopia, blurred vision, blepharoptosis, and photophobia caused by loss of papillary light reflex, but may be preceded by GI symptoms, such as nausea, vomiting, abdominal pain, and diarrhea. Other common symptoms are generalized weakness, dysphagia, dysarthria, nasal voice, and constipation caused by paralytic

ileus. The diagnosis of botulism is based on compatible clinical findings and history of exposure to suspect foods and is confirmed by detection of toxin in serum, stool, or gastric contents of the patient or in leftover fish. Differential diagnosis includes the Guillain-Barre syndrome, myasthenia gravis, basilar meningitis, and stroke.²¹ *C. botulinum* involves seven types of toxins and type A, B, and E usually are involved in human poisoning. Botulism from seafood products is most frequently caused by type E toxin.

The bacterial spores are highly heat resistant and may not be inactivated by boiling for several hours; however, commercial canning procedures that use moist heat at temperatures above 121°C will kill the spores. Although the majority of reported cases of botulism have been associated with the consumption of inadequately processed home-canned food, ~10% of outbreaks have resulted from contamination of commercially canned fish. Toxins are readily destroyed by heat and are inactivated by boiling for 10 minutes or by heating at 80°C for 30 minutes. The toxins are zinc metalloproteinases that cleave specific components of the synaptic membrane docking and fusion complex and thus prevent the release of acetylcholine at the neuromuscular junction and autonomic synapses.²² Treatment should include close medical supervision, supportive care, and early use of trivalent equine antitoxin (types A, B, and E) and GI decontamination.

Staphylococcal Food Poisoning

Acute gastroenteritis is caused by the ingestion of food contaminated with preformed staphylococcal enterotoxin. The onset is abrupt and ranges from 2 to 8 hours postingestion and symptoms start with characteristically severe nausea and vomiting, which are present in most cases. Other symptoms may include abdominal cramps, diarrhea, and occasionally headache and fever. The attack is brief, most often lasting only 3–6 hours, and recovery is complete but in severe cases it may lead to dehydration, prostration, and shock. Diagnosis is clinical and can be confirmed by presentation of coagulase-positive staphylococci in the suspected food or vomitus. Treatment is symptomatic.²³ Fish along with cream pastries, milk, processed meat, and mayonnaise provide excellent media and if contaminated and allowed to remain at room temperature, these organisms can multiply rapidly and produce toxins.

BACTERIAL AND VIRAL INFECTIONS

Vibrio Species

Nine marine *Vibrio* species have been associated with food-borne disease in humans. *Vibrio cholera* infection is most prevalent during the summer months. It is characterized by abrupt onset and watery-type diarrhea; vomiting occasionally occurs. A persisting reservoir along the Gulf coast may continue to cause sporadic cases.²⁴

Vibrio parahaemolyticus is found in coastal waters

throughout the world. In the United States, it has been related to inadequately cooked seafood, usually shrimp and crayfish.²⁵ *V. parahaemolyticus* damages the intestinal mucosa and the stool may be bloody. Diarrhea develops 12–48 hours after ingestion of contaminated food. Chills and fever are observed in over one-half of the cases. Of patients with acute *V. parahaemolyticus* gastroenteritis, 88% reported having eaten raw oysters during the week before their illness occurred. The median attack rate among persons who consumed the implicated seafood was 56%.²⁶

Although quite rare, infection of immunocompromised persons with *Vibrio vulnificus* can be associated with high mortality (50%). It appears to be part of the normal bacterial flora of estuaries along the United States Gulf, Atlantic, and Pacific coasts. The septicemia induced by *V. vulnificus* is associated with eating raw oysters.

Norwalk Virus

In the United States ~55% of the reported shellfish-related incidents are registered with unknown etiology but mainly are believed to be caused by Norwalk, Norwalk-like, or human enteric virus infections, with a smaller proportion caused by vibrio bacteria. The incubation period generally is 24–48 hours. The most common symptoms are nausea, vomiting, diarrhea, and abdominal cramping and are of brief duration and resolve within 24–48 hours.²⁷ The diagnosis is clinical, with typically unrevealing bacterial studies on stool and shellfish specimens. It can be confirmed by presentation of seroconversion and the formation of immunoglobulin M antibody to Norwalk virus. Shellfish-borne disease occurs mostly from mollusks consumed raw or lightly heated.

Finally, marine organisms such as oysters may concentrate microorganisms including hepatitis A.²⁸ Contamination occurs through collection of shellfish grown in sewage-polluted waters or by contaminated waters used in irrigation, as well as through infection of foods by food handlers.

CONCLUSIONS FOR THE ALLERGIST

This review presents the more common clinical syndromes produced by the ingestion of natural seafood toxins.²⁹ For the practicing allergist, knowledge of this wide array of toxic syndromes is important for the proper differential diagnosis of seafood allergy. A careful history and physical exam are essential to establish the diagnosis on clinical grounds, which can be confirmed by detection of toxins either in remnants of the seafood or in specimens collected from the patient. The history should include the severity of the symptoms, time of the last reaction, frequency of reactions, whether others became ill, previous history of food allergy, types of marine species ingested, and where they were captured, and the quantity of food

consumed and the way in which it was prepared. Whether the food was eaten at a restaurant, whether the patient was traveling, alcohol was consumed, and medications taken by the patient should be recorded also.

Presence of similar symptoms in other individuals who shared the seafood meal and the "endemic" nature of the syndrome are paramount in alerting the physician to possible seafood poisoning. The absence of prior reactions to the same seafood and its subsequent tolerance without symptoms point away from an allergic etiology and should be considered as corroborative evidence in support of a toxic syndrome. Because histamine mediates the symptoms of both scombroid and type I hypersensitivity reactions, clinical manifestations of scombroid virtually may be indistinguishable from seafood allergy.

Neurological symptoms associated with an allergic reaction are the result of hypoperfusion of the central nervous system and correlate with the severity of cardiovascular involvement and hypotension in anaphylaxis. This may help the physician to distinguish ciguatera, PSP, NSP, and ASP, where neurological impairment is commonly present in the absence of hypotension. In ciguatera, knowledge of the type of fish, which is either imported from or consumed in endemic areas such as the Caribbean, Hawaii, and the Pacific Islands, will provide clinical information to differentiate it from seafood allergy. Likewise, in puffer fish poisoning, consumption of fugu, a delicacy of Japanese cuisine, and in shellfish poisoning, the location where seafood was caught, *e.g.*, the Pacific Coast in cases of PSP and ASP, are crucial pieces of information. The seasonal association with algal blooms and the presence of high levels of biotoxins or toxic algae that are reported by authorities surveying coastal waters should increase the index of suspicion for physicians practicing in endemic areas. In the majority of these toxic syndromes, the causative toxin does not alter the taste and appearance of the seafood and is not inactivated by normal cooking.

Treatment is supportive, with active early respiratory support, especially in cases where neurological involvement could lead to respiratory paralysis. Upper respiratory reactions in individuals with no history of atopy and exacerbation of chest symptoms in asthmatic patients are caused by aerosolized NSP toxins. These irritative reactions that usually are associated with a red tide and have occurred on the Atlantic coast should not be mistaken for allergic respiratory symptoms.

Viruses, bacteria, and bacterial toxins may cause GI and systemic symptoms that can be confused with food allergy. Raw or lightly steamed shellfish and raw fish, *e.g.*, sushi, are potential sources of infection with hepatitis-A and Norwalk virus and *Vibrio* sp. Botulism is a hazard associated with consumption of home-canned, vacuum-packed smoked, or unviscerated salt-dried fish. If alternative diagnoses can not be ruled out and seafood allergy remains a likely diagnosis, a skin-prick test and oral food challenge

are diagnostic procedures of choice that may be used in the evaluation of the patient.

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