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Harmful Algal Blooms and Public Health

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Abstract

The five most commonly recognized Harmful Algal Bloom related illnesses include Ciguatera poisoning, Paralytic Shellfish poisoning, Neurotoxin Shellfish poisoning, Diarrheic Shellfish Poisoning and Amnesic Shellfish poisoning. Although they are each the product of different toxins, toxin assemblages or HAB precursors these clinical syndromes have much in common. Exposure occurs through the consumption of fish or shellfish; routine clinical tests are not available for diagnosis; there is no known antidote for exposure; and the risk of these illnesses can negatively impact local fishing and tourism industries. Thus, illness prevention is of paramount importance to minimize human and public health risks. To accomplish this, close communication and collaboration is needed among HAB scientists, public health researchers and local, state and tribal health departments at academic, community outreach, and policy levels.

Introduction

There is a growing appreciation of the importance of Harmful Algal Blooms (HAB's) and HAB related illnesses to public health. With the dramatic increase in the number of harmful algal blooms, as well as their frequency and intensity in coastal regions throughout the world (Glibert et al., 2005), there are more toxic algal species, more algal toxins and more geographic areas affected than ever before. Often attributed to natural environmental factors (hurricanes, earthquakes); anthropomorphic activity (increased eutrophication, marine transport and aquaculture) and climate change (Lehane and Lewis, 2000; Pratchett et al., 2008; Badjeck et al., 2010), when these toxic species proliferate, they may cause massive fish skills, destroy or poison shellfish beds, and contribute to wildlife mortality, human illness and death. The risk of HAB-related illnesses is further amplified by shifting preferences to heart-healthy diets, increased travel to coastal destinations, increased consumption of imported fish, the growth of coastal urban communities and growing segments of the population involved in marine recreation (Jensen, 2006; Ralston et al., 2011). Thus, in the absence of ongoing public health surveillance, research and outreach into

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HAB related exposures and illnesses, it is anticipated that the number of cases of HAB related illnesses will continue to rise over the next decade. With this in mind, this Special Issue of Harmful Algae is devoted to HABs and public health.

With the exception of aerosolization of the "Florida Red Tide" (*Karenia brevis* blooms), the primary vector for HAB related human health concerns is the consumption of fish and shellfish. Often due to the activity of HAB related toxins, seafood consumption has become the leading cause of food-borne illness with known etiology. It is responsible for 10-20% of outbreaks among all food types and about 5% of all individual illnesses (Huss et al., 2004, CSPI, 2007). The annual acute care costs of seafood born disease are estimated up to two-thirds of a billion dollars (Ralston et al., 2011). Persistent symptoms are seen in about 2-3% of cases and the costs of medical care, lost productivity and functional disability associated with chronic sequelae are thought to exceed those of acute care. These are conservative estimates as there is considerable diagnostic uncertainty and underreporting with respect to seafood related illnesses (Sobel and Painter, 2005; Flemming et al., 2011).

To orient the reader to the diverse scientific papers to follow, this article is organized around the 5 most commonly recognized HAB related illnesses. This will include a general description of Ciguatera Poisoning, Paralytic Shellfish Poisoning, Neurotoxin Shellfish Poisoning, Diarrheic Shellfish Poisoning (DSP), and Amnesic Shellfish poisoning with a quick reference table (Table 1). An overview of HAB's from a public health perspective will follow as well as highlights for important areas for future research.

Ciguatera Fish Poisoning (CFP)

It is generally well accepted that Ciguatera Fish Poisoning (CFP) is the most frequently reported seafood-related disease in the United States and most common foodborne illness related to finfish consumption in the world (Isbister and Kiernan, 2005; Lynch et al., 2006; Friedman et al., 2008; Kumar-Roiné et al., 2011). It is endemic in areas where consumption of reef fish is common. This includes the Caribbean, southern Florida, Hawaii, the South pacific and Australia. However, emerging data suggests expansion of the biogeographical range ciguatoxic fish (Villareal et al., 2007; Bienfang et al., 2008; Dickey and Plakas, 2010) with reports of CFP from fish originating in South Carolina and the Northwestern Gulf of Mexico (CDC, 2006).

CFP is caused by the consumption of reef fish that have accumulated potent neurotoxins (ciguatoxin) in their flesh and viscera. The toxins are produced by the marine dinoflagellate, *Gambierdiscus,* that live on various, sometimes harmful microalgae in coral reef ecosystems. Herbivorous fish consume these dinoflagellates and through bioaccumulation and magnification the toxin advances through the food web via carnivorous species. More than 400 fish species are thought to have the potential for ciguatera toxicity (Halstead, 1978; Lehane and Lewis, 2000). However, the risk is greatest for carnivorous, predatory fish, such as barracuda (of which >70% may be toxic). Other high risk fish include snapper, grouper and amberjack, (Langley et al., 2009).

The diagnosis of ciguatera fish poisoning (CFP) or “ciguatera” is typically based upon clinical symptoms within the context of a carefully elicited history of recent predatory reef fish consumption. Symptoms of CFP arise within 12 hours of eating the toxic fish. The initial symptoms begin with severe gastrointestinal problems (nausea, vomiting, diarrhea, abdominal pain) which usually abate within 24 hours (Hokama, 1988). Cardiovascular problems (generally a combination of bradycardia with hypotension) and/or neurologic symptoms may also accompany this acute episode. In the Caribbean and S. Florida cardiovascular disorders often reverse within 48 to 72 hours (Hokama 1988; Butera 2000). However, in Pacific regions outcomes may be less favorable as there have been reports of rapid progression to respiratory distress, coma and death (Lange 1987; DeFusco et al., 1993; Habermehl et al., 1994). From a few hours to two weeks after exposure, a diverse range of subjective neurological complaints have been reported in about 70% of cases (Lawrence et al., 1980). These may include pain and lower extremity weakness; painful tingling around the mouth, teeth, nose and throat; peripheral paresthesia, headache, metallic taste, hyporeflexia, and/or dysphagia. The hallmark of CFP neurological symptoms is an unusual paradoxical disturbance of thermal sensation, ie., cold objects feeling hot and sometimes hot feeling cold (Pearn, 2001; Achaibar, 2007). Although detailed case reports document a wide range of neurologic symptoms, the full symptom complex of CFP remains to be fully characterized or understood.

Recovery from acute neurologic symptoms is longer and less predictable than gastrointestinal or cardiac symptoms which persist from approximately one week to six months (Lange, 1992; Butera et al., 2000; Achaibar, 2007). In addition, there are many patients who report symptom persistence for many years. The chronic ciguatera syndrome is typically characterized by intractable fatigue, weakness and/or paresthesias and accompanied by depression. Chronic symptoms may be present continuously or reappear after a period of presumed recovery. This recurrence may also be triggered by alcohol use or repeated consumption of fish with low levels of ciguatoxin. This suggests that persons who have had one episode of ciguatera are at increased risk for repeated illness (Morris et al., 1982). In this special issue, Lopez et al. (in press) report their efforts toward developing a conceivable biomarker for chronic and recurrent ciguatera.

Paralytic Shellfish Poisoning (PSP)

Paralytic shellfish poisoning (PSP) is a potentially lethal clinical syndrome. It is caused by eating bivalve mollusks (mussels, scallops and clams) contaminated with a group of structurally related marine toxins collectively referred to as saxitoxins or STX (Shumway, 1990; James et al., 2010). PSP toxins are concentrated in the shellfish as a result of the continuous filtration of toxic algae produced by several dinoflagellates (including *Alexandrium*, *Gymnodinium* and *Pyrodinium*) during “red tide” blooms. Predators of bivalve shellfish (scavenging shellfish, lobsters, crabs and fish) may also be vectors for saxitoxins, thus expanding the potential for human exposure (Halstead and Schantz, 1984). Geographically, the most risky regions for PSP are cold water marine coasts. This includes Alaska, the Pacific Northwest and St. Lawrence region of Canada in North America. Toxic shellfish have also been found in cold water regions of southern Chile, England, Japan and the North Sea.

The initial symptoms of PSP are numbness or tingling around the mouth and lips within 10 minutes to two hours after shellfish consumption. The timing of symptom onset is thought to be dose dependent (Gessner et al., 1997a; McLaughlin et al., 2011). In mild cases, this may be the only symptom. However, in more severe cases, the numbness and tingling spread to the neck and face and may be accompanied by headache, abdominal pain, nausea, vomiting, diarrhea and a wide range of neurologic symptoms. These neurologic symptoms may include weakness, dizziness, dysarthria, paresthesia, double vision, loss of coordination, vertigo or dizziness, and/or a "floating" sensation. In the most severe cases, symptoms rapidly progress to severe respiratory problems in a person who otherwise exhibits no evidence of respiratory difficulty (Gessner et al, 1997b) and death may result. In most cases, recovery is rapid and complete with most symptoms resolving within twenty-four to seventy-two hours with fourteen days representing the maximum recovery window (Rodrigue et al., 1990; Gessner et al, 1997a). Given the potential severity of the illness, early diagnosis is essential.

Neurotoxic Shellfish Poisoning (NSP)

Neurotoxic Shellfish Poisoning (NSP) is typically caused by ingesting bivalve shellfish (clams, oysters and mussels), contaminated with brevetoxins. The risk for NSP toxins in shellfish is associated with HABS or "red tides" along the Gulf of Mexico. The greatest number of cases appear to come from the west coast of Florida, although this may be due to differences in surveillance rather than actual differences in occurrence (Daranas et al., 2001; Watkins et al., 2008). Due to careful monitoring, most cases of NSP that occur in the US are associated with recreationally-harvested shellfish collected during or post "red tide" blooms (Fleming et al., 2011). Similar to other HAB related illnesses, there is an ongoing threat of new NSP cases as harmful algal blooms may be transported to new regions. And in fact, the largest number of reported U.S. cases came from a single outbreak of 48 persons in North Carolina whereby brevetoxin-producing organisms were transported up the eastern seaboard (Morris et al., 1991). Harmful algal blooms and associated outbreaks of NSP have also been reported in New Zealand and Mexico (Ishida et al., 1996; Sim and Wilson, 1997; Hernández-Becerril et al., 2007).

The diagnosis of NSP is based upon clinical presentation and history of bivalve shellfish consumption from a risky area. Symptom onset may range from a few minutes to 18 hours after consuming contaminated shellfish, however in most cases, time to illness is about three to four hours (Morris et al., 1991; Poli et al., 2000). The symptoms of NSP include both gastrointestinal and neurological problems. The most frequently reported symptoms are nausea, vomiting, abdominal pain, and diarrhea. However, these are often not the primary presenting complaint. Of greater concern to most individuals are the neurological symptoms which may include paresthesia of the mouth, lips, tongue; peripheral tingling, partial limb paralysis, slurred speech, dizziness, ataxia and a general loss of coordination. Reversal of hot/cold sensation, similar to ciguatera poisoning has also been reported (Arnold, 2011). The most common symptoms from the North Carolina outbreak were paresthesias (81%), vertigo (60%) malaise (50%), abdominal pain (48%), nausea (44%), diarrhea (33%), weakness (31%), ataxia (27%), chills (21%), headache (15%), myalgia (13%) and vomiting (10%) (Morris et al., 1991). Albeit rare, a few cases have reported respiratory discomfort and

distress, some requiring ventilator support (Watkins et al., 2008). Although hospitalization is sometimes necessary, no fatalities have been reported as a result of NSP (Arnold, 2011). Most patients recover within two to three days without long term or chronic effects (Baden, 1983; Morris, et al., 1991; Watkins et al., 2008).

Recent studies suggest that aerosolization of the toxin from sea water produces a transient, self-resolving inhalational syndrome characterized by respiratory problems and eye irritation (Flemming et al., 2005). Exposure has been associated with wave action and aerosolized sprays along Florida beaches during “red tide” events. Adverse respiratory effects include upper airway irritation and discomfort, decreases in pulmonary function and exacerbation of symptoms in people with asthma.

Amnesic Shellfish Poisoning (ASP)

The potential risk of Domoic Acid (DA) to human health was discovered in in 1987 in Montreal, Canada (Perl et al., 1990 a,b; Teitlbaum et al., 1990a,b). Persons who ate affected blue mussels harvested from the Prince Edward Island region suffered serious medical illnesses and in some cases death. Survivors were left with a permanent and profound memory disorder, Amnesic Shellfish Poisoning (ASP). The rapid work of scientists, largely dependent on animal models, led to establishing safety standards for DA for shellfish harvesting and consumption both in the U.S. and Canada. Aggressive monitoring by national and state health fisheries and food and drug agencies appears to have been effective in preventing further deaths by closing shellfish beds if DA levels exceeded 20 ppm. Within the past 15 to 20 years, measured DA levels have been significantly elevated on the U.S Pacific coast (Walz et al., 1994; Wekell et al., 1994; Trainer et al., 1998; Grant et al., 2010). Persistent low levels in some coastal areas have been interspersed with dangerously high levels, responsible for increases in toxicity affecting fish, shellfish, shorebirds and sea lions in California, Washington and Oregon (Sierra-Beltrán et al., 1997; Scholin et al., 2000; Gulland et al., 2002; Beasley, 2003; Goldstein et al., 2008). The extent to which chronic low level exposure impacts human health remains to be determined. Preliminary findings from Grattan et al., (in press) in this issue raise the possibility that milder memory problems may be associated with lower level, chronic exposures in adults who are heavy consumers of razor clams. Thus, domoic acid neurotoxicity may potentially be associated with a non-amnesic syndrome.

DA is a naturally occurring toxin produced by blooms of P*seudo-nitzschia*. Shellfish and other marine organisms feed on Pseuto-nitzschia and concentrate the toxin within them. Hence, the shellfish become toxic to the wildlife and people that consume them. Although domoic acid has been found in the viscera of Dungeness crab and other organisms, razor clams are one of the most significant vectors as they can hold the toxin for up to one year in the natural environment, or several years after being processed, canned or frozen (Wekell et al., 1994).

Clinical diagnosis is largely based upon symptom complaints and eliciting a detailed history of recent shellfish consumption. Acute symptomatology of high level exposures include vomiting, abdominal cramps, diarrhea, headache, seizures, respiratory excretions, confusion

coma and in some cases, death (Pearl et al., 1990a,b; Teitelbaum et al., 1990a,b). In the Prince Edward Island outbreak, the most severe neurological sequelae were found in males, over 60 years of age with symptom onset within 48 hours of ingestion. In the younger age groups, the most vulnerable individuals were those with preexisting illnesses such as renal disease, hypertension or diabetes. Complete recovery occurred in a few cases, for others severe memory problems (amnesia) persisted and in one case, the delayed onset of temporal lobe epilepsy was observed (Cendes et al., 1995).

Diarrheic Shellfish Poisoning (DSP)

Diarrheic shellfish poisoning is characterized by acute gastrointestinal symptoms triggered by the ingestion of shellfish contaminated with okadaic acid and related toxins. Mussels, clams, scallops and oysters are the most common vectors for the DSP toxins which are produced by a community of dinoflagellates, most notably, *Dinophysis* spp and *Prorocentrum* spp (James et al., 2010; Valdiglesias et al., 2011). Outbreaks of DSP have been reported in Japan, France, other parts of Europe, Canada, New Zealand, United Kingdom, and South America (Yasumoto et al., 1978; Kawabata, 1989; Belin, 1991; van Egmond et al., 1993; Hinder et al., 2011). There have not been any confirmed cases of DSP in the United States. However, the responsible organisms (*Dinophysis* spp) have been identified in Texas Gulf coastal waters and oysters in that region reportedly tested positive for okadaic acid (Barbier and Diaz, 2003; Deeds et al., 2010).

Similar to other shellfish illnesses, the diagnosis of Diarrheic Shellfish Poisoning is largely made by dietary history and symptoms. Symptom onset typically occurs within 30 minutes to 4 hours after eating contaminated shellfish. The main symptom is incapacitating diarrhea, followed by nausea, vomiting and abdominal cramps (James et al., 2010). The symptoms may be severe and lead to dehydration, but are usually self-limiting and continue for about three days. Although DSP poisoning is traditionally believed to result in full recovery, preliminary data raises the possibility that DSP toxins may be associated with more significant medical problems over time.

Discussion and Future Directions

There are five commonly recognized HAB related illnesses: Ciguatera Fish Poisoning, Paralytic Shellfish Poisoning, Neurotoxic Shellfish Poisoning, Amnesic Shellfish Poisoning and Diarrheic Shellfish Poisoning. At this time, routine, clinical diagnostic tests are not available for any of them. Diagnoses are largely based upon symptom presentation and history of seafood consumption. Once diagnosed, there is no antidote for any of the HAB related toxins. Therefore, symptom management and supportive care are the only available treatments. With this in mind, illness prevention is of paramount importance to manage HAB-related human and public health risks. This necessitates close communication and collaboration between HAB scientists, public health researchers and local, state and tribe health departments at academic, community and policy levels. The prevention of HAB-related illnesses would also be advanced with future laboratory, oceanographic, epidemiological, economic, and social-psychological, research to increase environmental monitoring; identify specific biomarkers for human illness; further characterize HAB related

syndromes; identify at-risk individuals and communities; develop interventions at the individual and community levels; enhance outreach effectiveness; improve reporting and illness surveillance programs; and contribute to policy development.

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Table 1

Seafood Intoxications

Syndrome (Major Toxin)	Vectors (Known and Potential)	Onset Time and Duration	Major Symptoms	Treatment	Prevention
Ciguatera Fish Poisoning[a] (Ciguatoxin)	Large, predatory tropical reef fish (barracuda, grouper, red snapper, amberjack); some types of eels; farm-raised fish that feed on contaminated fish.[b]	12 to 24 hours; neurological symptoms can last months to years	**n, v**, **d**, **ab**, **p** (especially hands and feet), **t**, **bp**. Also: metallic taste, itching, dizziness. Possible recurrence of neurological symptoms during times of stress, after ingesting alcohol or low level fish. Low mortality in the US.[c,d,e]	Supportive. Mannitol therapy is recommended for neurological symptoms.[f] Brevenal has also been indicated.[g]	Avoid consuming risky fish; education about avoiding consumption of the viscera especially where reef fish are a key subsistence source[h]; monitoring; illness surveillance[i]
Diarrhetic Shellfish Poisoning[j,k,l] (Okadaic Acid)	Mussels, oysters, scallops, clams, cockles, some species of crabs [m,n,o]	30 minutes to 15 hours; full recovery, within 3 days[m]	**d** (incapacitating), **n**, **v**, **ab**. Headache, fever. No reported mortality.	Supportive. Most people do not seek medical treatment.	Monitoring seafood and water; regulated in European countries, though outbreaks still occur[p]
Neurotoxic Shellfish Poisoning[q] (Brevetoxins)	Mussels, clams, whelks, conch, coquinas, oysters, scallops; liver and stomach contents of some planktivarous fish; inhalation of toxin aerosolized by coastal wind and waves[q,r]	*Consumption:* A few minutes up to 18 hours (often within 3-4 hours) *Inhalation:* Minutes to hours (<24 hours)	*Consumption:* **p** (perioral, face, extremities), **ab**, **t**, **d**, **b**, **r** (most severe cases). May appear disorientated or intoxicated (slurred speech, pupil dilation, overall fatigue, involuntary muscle spasms). *Inhalation:* **a**, **b**, **r**. Throat irritation, sneezing, coughing, itchy and watery eyes, burning of upper respiratory tract. No reported mortality for either pathway's	*Consumption:* Supportive. *Inhalation:* Leave the beach and go to an air-conditioned area.	Coastal and seafood monitoring and quarantine; clear, easily available information on recreational closures[s,t]; persons with asthma or respiratory problems should avoid beaches during "red tides."
Paralytic Shellfish Poisoning[u,v,w] (Saxitoxins)	Scallops, mussels, clams, geoducks, cockles, puffer fish, some fish, gastropods, crustaceans[x]	30 minutes to 3 hours; a few hours to a few days	**p** (perioral, often spreading to neck and extremities), **n**, **v**, **r** (severe doses: respiratory paralysis and death). Muscular weakness, drowsiness, incoherent speech. No mortalities in recent US and European outbreaks.	Supportive. Artificial ventilation in severe cases.	Coastal monitoring; quarantine of seafood and region; rapid case reporting; beach closures to recreational harvester[y]
Amnesic Shellfish Poisoning[z,aa] (Domoic Acid)	Razor clams, mussels, oysters, squid. Viscera (not muscle) of scallops, sardines, anchovies, crab, and lobster.[bb]	Within 48 hours; months to years with permanent amnesia.	**ab**, **n**, **v**, **r**, disorientation, seizures, permanent short-term memory loss, possible neurodevelopmental delay. Excessive respiratory secretions.[cc] Coma and death only among most	Supportive.	Coastal monitoring of water and shellfish; harvesting beach closures; rapid illness reporting

Syndrome (Major Toxin)	Vectors (Known and Potential)	Onset Time and Duration	Major Symptoms	Treatment	Prevention
			severe cases[y] or elderly.[bb]		

Abbreviated symptoms: **a**, allergic-like; **ab**, abdominal cramps; **b**, bronchoconstriction; **bp**, decrease in blood pressure; **d**, diarrhea; **n**, nausea; **p**, parathesias; **r**, respiratory distress; **t**, reversal of temperature sensation; v, vomiting

[a] Barbier and Diaz, 2003

[b] DiNubile and Hokama, 1995

[c] Hokama, 1988

[d] Kumar-Roiné et al., 2011

[e] Morris et al., 1982

[f] Dickey and Plakas, 2010; see also for treatment for specific symptoms

[g] Nguyen-Huu et al., 2010

[h] Copeland et al., 2014

[i] Tester et al., 2013

[j] Hossen et al., 2011

[k] Taylor et al., 2013

[l] Valdiglesias et al., 2013

[m] James et al., 2010

[n] Manerio et al., 2008

[o] Vale and Sampayo, 2008

[p] see [j] and Cordier et al., 2000

[q] see for examples: [j,o], and Hinder et al., 2011

[r] Hoagland et al., 2014

[s] Plakas and Dickey, 2010. See Terzagian, 2006 for examples

[t] Reich et al., 2015

[u] Etheridge, 2009

[v] Cusick and Saylor, 2013

[w] Hurley et al., 2014

[x] Deeds et al., 2008

[y] for examples, see [c] and McLaughlin et al., 2011

[z] Grant et al., 2010

[aa] Péréz-Gómez and Tasker, 2014

[bb] Lefebvre and Robertson, 2010

[cc] Teitelbaum et al., 1990a,b; Perl et al., 1990a,b