THE NORTHERN HOSPITAL

CIGUATERA POISONING

"Big Fish Eat Little Fish", engraving Pieter van der Heyden; after a drawing by Pieter Bruegel the Elder, Flanders 1557, Metropolitan Museum, New York City.

In 1557 the Dutch engraver Pieter van der Heyden produced the famous print, "Big Fish Eat Little Fish", a depiction of a well known Dutch proverb of the Sixteenth century. It was published by Hieronymus Cock in Antwerp, as shown by the inscription on the bottom right. This proverb held particular resonance for the Dutch in the context of their seaborne business enterprises, which would usher in the Golden Age of empire in the Seventeenth century. In the boat in the foreground a fisherman instructs his young son, "See the big fish eat the little fish". He points to a fantastic whale sized fish, being cut

open by a helmeted figure with an improbably large knife. Out spills a huge cache of smaller fish, many of which have consumed yet smaller fish down the line of the "food chain". The fisherman's companion is himself in the process of cutting open a fish to reveal another smaller fish. The message the fisherman is giving his son is quite clear. The text below the main frame translates as, "the rich oppress you with their power". The world of business is a cutthroat place to live! We know on both stylistic grounds as well as hard documentary evidence that the image was the work of the Dutch painter Pieter Bruegel the Elder. The original unsigned but well authenticated ink drawing of Breughel of 1556 survives (Albertina, Vienna) - so art historians know that it was Bruegel that produced the original image. In his more famous work, the astounding "Netherlandish Proverbs" produced two years later in 1559, we see the motif reproduced again amidst the profusion of at least a hundred other proverbs.

However we find a curious inscription at the bottom left of the image, "Hieronijmus Bos inventor". This of course seems to indicate that the earlier painter - the most enigmatic Hieronymus Bosch, (c. 1450-1516) was the true original artist - not Breughel. Two counter arguments prevail today. The first being that in 1557, Bruegel was a small time, relatively unknown designer of prints, whose fame had not yet come. In this year Hieronymus Bosch was far more famous, the implication being that the publisher wished to attribute his print to the more famous artist, and by doing so presumably enhance the value of his product. A little unfair to Bruegel of course, but "business is business" and big fish eat little fish after all! And yet, when one examines the work in fine detail, something startling appears. For those who know the works of Bosch well, we see many of his mysterious and startling motifs recreated in Breughel's work. There is no doubt at all that Bruegel in many of his later works drew on the enigmatic motifs of Hieronymus Bosch - the gigantic proportions of otherworldly animals, unnatural fish that fly, have legs, emerge from shells, or appear as monstrous hybrids of other animals or even humans, helmeted figures with horrifyingly large razor sharp knives that cut into flesh, and faceless hooded figures climbing up ladders. So should we feel sorry for Bruegel? - probably not - he took many of his motifs from Bosch, who very probably was, if not the complete inventor, then at least the partial inventor of "Big Fish Eat Little Fish". The most we can say about Bruegel in regards to this famous work is that he at least took the hellish Dantean motifs of Bosch, and presented them in novel ways.

In Breughel's work we see the clear message of the dangers of the world in general and business in particular, but we may also perceive a medical danger from it as well. The dinoflagellate microorganism Gambierdiscus toxicus, lies close to the base of the food chain. This organism can produce a potent neurotoxin, and as bigger fish eat smaller fish this toxin can be carried up this food chain all the way to humans!

"Hieronijmus Bos inventor", detail, "Big Fish Eat Little Fish".

CIGUATERA POISONING

Introduction

Ciguatera poisoning is a fish borne toxinological syndrome.

It results in a predominantly **gastrointestinal** and **neurological** syndrome, which may rarely be fatal.

Ciguatera toxins are produced by **dinoflagellates** that are associated with **algae**.

The algae are consumed by herbivorous fish and these fish are consumed by larger carnivores. The toxins undergo varying extents of biotransformation as they pass through the marine food chain and may ultimately be consumed by humans.

There is no specific antidote, treatment is supportive.

The condition can be mild, moderate or severe.

In severe cases symptoms can be prolonged for weeks to months, and in some cases there are permanent sequela.

History

The current name of the affliction is derived from "cigua" a Spanish term for a Caribbean marine turban shell, *Turbo pica*, which can cause a similar toxic effect after ingestion. [3]

In 1774 Captain James Cook and his crew suffered from ciguatera fish poisoning on two occasions while in the New Hebrides region. The species thought to be responsible was the red bass, *Lutjanus bohar*. [3]

Epidemiology

Ciguatera is usually associated with coral reef habitats and is particularly prevalent in areas that have experienced some form of ecosystem disruption such as industry, cyclones coral bleaching triggered by rising water temperatures through the insidious effects of climate change.

These events cause coral reef damage which provides food for the toxic dinoflagellates implicated in ciguatera poisoning.

World wide ciguatera is the most common non-bacterial form of food poisoning associated with fish consumption.

See Appendix 1 below

Pathophysiology

Ciguatoxin:

Ciguatoxin is a **heat stable** and **acid stable** toxin produced by the motile photosynthetic **dinoflagellate** microorganism **Gambierdiscus toxicus**, (*after the Gambier Islands in French Polynesia where the initial discovery was made*).

Ciguatoxins are **not** affected by freezing, cooking or salting. They are also odorless, and tasteless.

There are about 30 species of dinoflagellates which produce bioactive compounds and some of these compounds rank as the most powerful non-proteinaceous poisons known

The principle dinoflagellate that may cause ciguatera are:

- Gambierdiscus toxicus (most common).

Other species implicated include:

- Amphidinium species
- Coolia monotis species
- Ostreopsis species
- Prorocentrum species.

The gambier-toxins, which are precursors to ciguatoxins, are produced only by certain strains of *Gambierdiscus toxicus* that live on a variety of macroscopic algae species that are eaten by small herbivorous fish.

The gambier-toxins are then bio-converted to ciguatoxins.

There are two main classes of ciguatoxins:

- The Pacific ciguatoxins
- The Caribbean ciguatoxins.

The difference between these toxins seems to account for the regional differences in the clinical effects of ciguatera. Pacific ciguatoxin-1 is *ten times more toxic* than the main Caribbean ciguatoxin, Caribbean ciguatoxin-1

Ciguatoxin accumulates in the flesh and organs of small fish. Such small fish are then consumed by larger predatory fish that further concentrate the toxins in their tissues. The

toxin is therefore progressively concentrated up the food chain, being mostly harmless to the fish host themselves.

Humans then become the final link in the food chain when they consume the larger fish.

Fish (especially large ones) may remain toxic for **years.**

Many fish species can accumulate ciguatoxin from time to time.

The most commonly implicated species of tropical **Australian** fish include:

- Narrow-barred mackerel
- Barracuda
- Coral trout.

Clinical Features

Although ciguatera poisoning is usually seen in tropical regions, more temperate regions are increasingly seeing cases due to:

- Travelers returning from ciguatera-endemic regions
- The consumption of contaminated imported fish.

In **severe** poisoning, paralysis can rapidly progress to respiratory failure.

Following ingestion of fish containing the toxin, the following symptoms occur:

1. Acute moderate to severe **GIT upset** within 1- 12 hours:
    - Nausea, vomiting, diarrhea and abdominal pain.
2. Pruritis/ rash may be seen, but not to the extent typical of scombroid poisoning.

*Following this within **12-72 hours** a descending neuroparalysis may occur:*

3. Non-specific "constitutional" symptoms can be significant.

    These may include

    - Arthralgias
    - Myalgias.

4 Sensory neurological symptoms:

The presence of sensory neurological symptoms in the *setting of fish ingestion* helps to differentiates ciguatera from other forms of food poisoning and gastroenteritis.

The following may be seen:

- *Initial* **peri-oral numbness** and **tingling** is very characteristic.
- Peripheral limb numbness, tingling
- Dysaesthesias:
    - ♥ Electric shock like shooting paraesthesias similar to L'hermitte's syndrome.
    - ♥ Cold allodynia:
        - ♥♥ This is pain produced by touching cold water or objects and is a very characteristic symptom.

          In broad terms allodynia is a pain response from a stimulus that does *not normally* provoke pain.

          Allodynia is classified based on the sensory modality that elicits the pain sensation; sensory modalities include touch (tactile allodynia), pressure and pinprick (mechanical allodynia) as well as both hot and cold (thermal allodynia).

          Note that cold allodynia is commonly *incorrectly* referred to as "reversal" of hot/cold temperature sensation.
- Ataxia

5. Rarely the syndrome can be fatal with:
    - CVS disturbances:
        - ♥ Arrhythmias and hemodynamic instability, most commonly in the form of **bradycardia and hypotension**.
    - Coma, seizures
    - Respiratory muscle paralysis.

Severity assessment:

The severity of symptoms is **dose-dependent**.

Ingestion of the fish's head, or viscera can cause more severe symptoms, as the toxin is more highly concentrated in these tissues.

Clinical severity can be classified as mild, moderate or severe as follows: [5]

Mild Ciguatera Toxicity	**Moderate Ciguatera Toxicity**	**Severe Ciguatera Toxicity**
Nausea/ vomiting/ diarrhoea	Dizziness	Asthenia (i.e lethargy/ malaise)
Pruritus	Myalgia/ arthralgia	Anxiety
Paresthesias	Cold allodynia	Bradycardia/ hypotension/ dysrhythmias
Headache	*Severe* diarrhoea/ severe vomiting	Vertigo/ Ataxia/ Visual blurring Delirium /stupor/ coma
	Abdominal pain	Respiratory failure

Natural history:

In geranial the prognosis is good with most patients making a full though slow recovery

The **gastrointestinal** symptoms normally resolve in **1 - 2 days**.

Paresthesias / neurological symptoms however often persist for 2 - 3 weeks.

In some cases however, neurological symptoms may persist for much longer - months or even years in severe cases.

There is sure no way to predict which patients will develop **chronic** symptoms, but chronic effects have most often been associated with:

Longer latency periods

- Symptom severity
- Longer duration of peak symptoms.
- When recognized and treated early, death is rare, (< 1 % of cases)

Factors affecting clinical features:

Both gastrointestinal and neurological effects after the consumption of fish is the hallmark of ciguatera, but the proportion of each type seems to be regionally dependent.

Neurological effects predominate in the Indo-Pacific region whereas gastrointestinal ones predominate in the Caribbean.

Symptoms may also occur with repeated fish exposure to sub-threshold toxin doses, suggesting a possible immunological mediated sensitization to the toxin, following an initial exposure.

Differential Diagnosis:

Differential diagnosis must also be borne in mind and may include:

1. Paralytic shellfish poisoning.

2. Scombroid poisoning

3. Tetrodotoxin poisoning, (muscular pain is not usually seen in tetrodotoxin poisoning.

4. Botulism.

5. Guillain-Barré syndrome.

6. Bacterial contamination of seafood may cause GIT upset but not neurocutaneous symptoms

Fever and other markers for sepsis (elevated white cell count and CRP) are **not** typical features of ciguatera poisoning.

Investigations

There is no current confirmatory test for the detection of ciguatoxin in humans. The diagnosis is therefore made on **clinical** and **epidemiological grounds**, with a history of ingestion of fish, followed by GIT upset and characteristic neurocutaneous and constitutional symptoms.

Note that fish that contain ciguatoxins do not smell, taste, or look any different from other non-toxic fish (of the same species).

ECG:

This may be done to look for evidence for cardiac involvement.

Ciguatera toxin testing:

Ciguatoxin testing on the suspected fish (if available), can be done at specialist centers.

Management

There is no specific antidote for ciguatera poisoning and so further treatment for any significant **circulatory** or **respiratory** complications in severe cases is **supportive**

1. Charcoal:

    - Gastrointestinal decontamination is not generally recommended.

      In very severe cases respiratory reflexes are depressed and so the risks will outweigh any potential benefit.

      In any case in the majority of cases the **delay** between ingestion of contaminated fish and the onset of symptoms and presentation precludes any benefit from decontamination.

2. IV fluid rehydration, as required.

3. Non-specific constitutional symptoms:

    - Simple analgesics such as aspirin, paracetamol, or NSAIDs can be used for non-specific constitutional symptoms such as headache, myalgias and arthralgias.

4. Pruritis:

    - Pruritus is treated with antihistamines.

5. Bradycardia / hypotension:

    - Uncommon cardiovascular complications such as bradycardia and profound hypotension will generally respond to fluid resuscitation and atropine/

      More severe cases require vasopressor and/or inotropic support.

6. Seizures:

    - Are treated according to usual protocols

7. Sensory neuralgic dysaesthesia symptoms:

Case reports suggest that neuropathic symptoms may be helped in some cases by anti-neuralgic medications including:

- Pregabalin:

  Two cases reports described the following regime: [6]

  - ♥ 75 mg daily titrated up to a maximum of 150 mg twice daily over three weeks.

    Maximal treatment was required for a total of around 12 weeks, after which the dose was weaned off over a period of a further 3 weeks.

- Gabapentin
- Amitriptylline

8. Avoidance of alcohol:

   - Alcohol consumption may increase the severity of the illness, and so should be avoided.

9. Respiratory failure will require mechanical ventilation.

10. Mannitol:

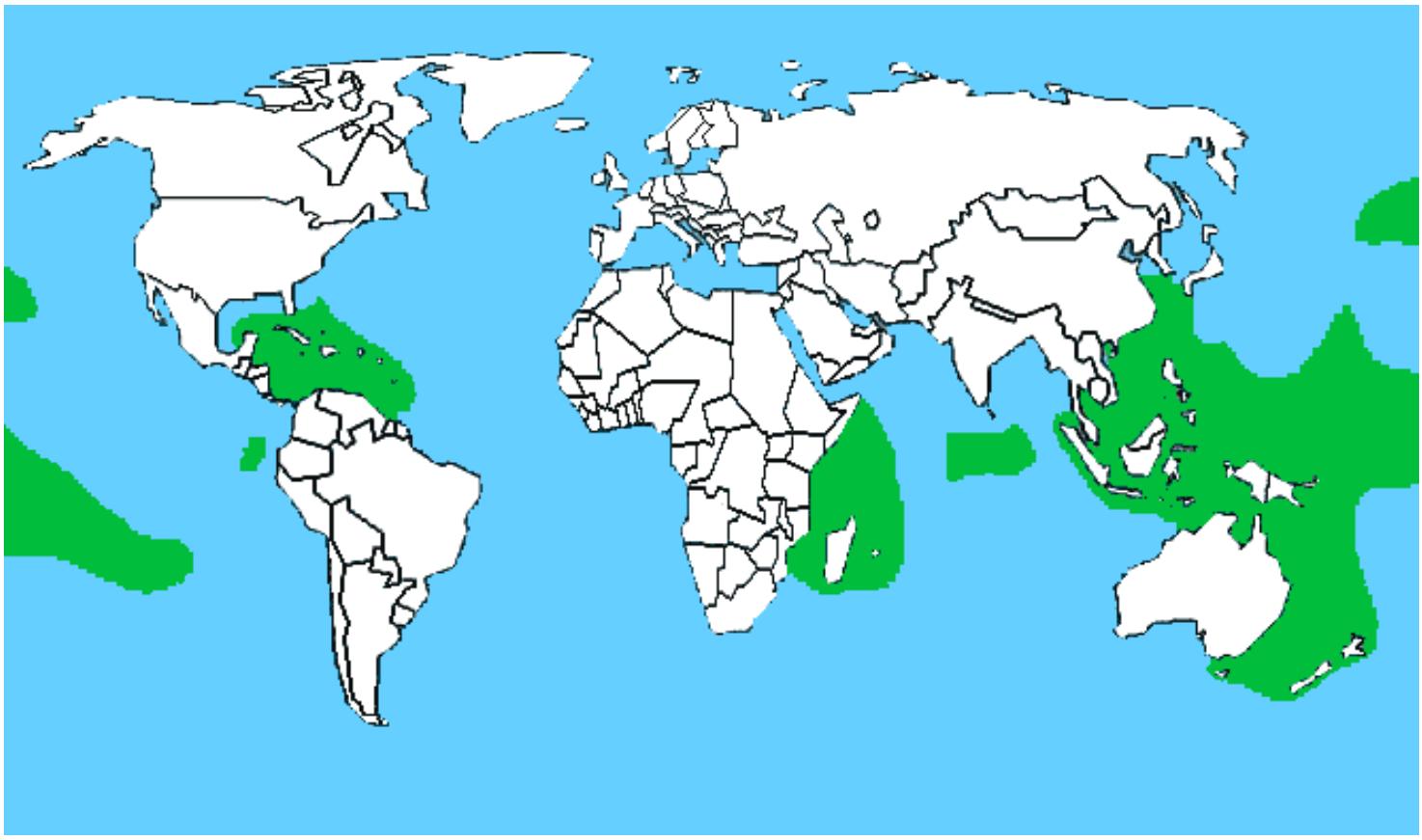
    - IV bolus dose mannitol was once widely advocated in the past; however it has been shown to be no more effective than normal saline and so is *no longer recommended*, (and will aggravate fluid losses). [1,2,4]

Disposition

As the condition is uncommon in Australia suspected cases should be discussed with a clinical toxinologist.

Any patient with **significant** neurological symptoms or any cardiovascular/ hemodynamic instability should be admitted.

Appendix1



Cases of ciguatera poisoning have a global, predominantly equatorial tropical and temperate distribution (between 35 degrees north and 35 degrees south) as shown above.

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