Title:

Climate Change and the Spread of Disease: An Illustrative Case of the First Australian Invasive Non-Toxigenic Vibrio Cholera Infection in a Newborn

Type of Manuscript:

Instructive Case

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Dr Jenny Hynson

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Nil

Case Report

An eight-week-old boy was transferred to a tertiary paediatric hospital in Melbourne, Australia from a rural hospital with seizures, altered conscious state and fevers. His parents reported that he was slightly unsettled the night prior and had one episode of loose bowel actions. He woke suddenly the following morning with an unusual cry and was found pale, eyes rolled back with postural stiffness.

The patient had been born at term by normal vaginal delivery with no antenatal issues. Maternal group B streptococcus status was negative. Immunisations were up to date and there were two other well siblings aged one- and two-years old. The family worked as cattle farmers on a rural property in northern Victoria.

Upon ambulance arrival, the infant required intramuscular midazolam to terminate seizures and intramuscular glucagon due to hypoglycaemia. In the emergency department (ED), he was hypothermic (35.5°C), hypoglycaemic (3.1mmol/L) and tachycardic (200bpm). On examination he was irritable, mottled, with a delayed capillary refill time of four seconds and had a slightly bulging anterior fontanelle. Pupils were equal and reactive. No rashes were observed.

Initial venous blood gas showed a pH 7.23 with lactate of 13mmol/L. C-reactive protein was 61 with a normal ammonia level. He had a further generalised tonic-clonic seizure in the ED, which terminated following a second midazolam dose and loading with intravenous (IV) phenytoin.

He required extensive fluid and glucose resuscitation and was empirically commenced on IV benzylpenicillin, cefotaxime, gentamicin, flucloxacillin, vancomycin and acyclovir.

Computed tomography (CT) of the brain performed prior to transfer showed hypodense thalami and basal ganglia (Figure 1). Subsequently the patient was intubated for transfer and dexamethasone and mannitol were added for neuroprotection.

Lumbar puncture after initiation of antibiotics revealed a cerebrospinal fluid white cell count of $1350 \times 10^6/L$ (normal range [NR] $0-5 \times 10^6/L$), ninety percent of which were neutrophils, with elevated protein ($>6.18g/L$; NR $0.20-0.40g/L$) and low glucose ($1.3mmol/L$; NR $2.8-4.0mmol/L$) and no growth on culture. The next day magnetic resonance imaging (MRI; figure 2) revealed acute necrotising meningo-encephalitis of the deep grey nuclei with an acute necrotising leukencephalitic component and early haemorrhage involving the bilateral hippocampi, brainstem and deep cerebellar white matter. On day three, blood cultures from the time of presentation grew a gram-negative bacillus, later identified as non-O1/non-O139 *Vibrio cholerae* sensitive to amoxicillin and gentamicin. Subsequently, high-dose

ciprofloxacin was added to benzylpenicillin, cefotaxime, gentamicin and acyclovir, the other antimicrobials having been ceased after transfer.

Further history revealed that the family used underground bore water for household bathing, including for bathing our patient. They drank only bottled water and the older children were known to suffer from diarrhoea after swimming in the bore water. The case was referred to the Department of Health and Human Services' Water Unit, however, testing was unable to be carried out.

The patient's clinical course had numerous complications including ongoing seizures, severe spasticity requiring baclofen and diazepam, acute renal failure, anaemia requiring blood transfusion, temperature instability and colitis. Somatosensory evoked potentials (SSEPs) showed absent cortical responses bilaterally. Interval MRI performed on day ten (figure 3) revealed progressive widespread necrosis through cortical and deeper structures with cavitation and new partially occlusive sinus venous thrombosis.

The antimicrobial regimen was rationalized to IV cefotaxime monotherapy on day seven and continued for a two-week course. The patient was extubated on day eleven. The family were made aware that the patient would likely be profoundly disabled should he survive into older childhood. He continued to be profoundly obtunded, had ongoing seizures and dystonia and

required feeding support via nasogastric tube. He was subsequently transferred back to the rural hospital with palliative care support. He passed away peacefully at home four months later.

Discussion

To our knowledge, this is the first documented case of invasive non-O1/non-O139 *V. cholerae* in a newborn in Australia (1). *Vibrio cholerae* is an environmental bacterium commonly found in estuarine and marine environments. The bacterium's O1 and O139 antigens encode the cholera toxin, which is responsible for causing secretory diarrhoea, the predominant feature of endemic cholera. Diarrhoeal cholera is still responsible for around 100,000 deaths annually (2), despite the availability of an oral vaccine against the O1 antigen.

The mainstay of management for diarrhoeal cholera involves rapid fluid replacement, zinc therapy, which has been shown to reduce the duration of diarrhea in children, and antimicrobial therapy in moderate to severe cases (3). Specific antimicrobial regimens are dependent on the patient's age. For patients above the age of eight, the World Health Organisation (WHO) and Centre for Disease Control (CDC) recommend tetracycline therapy (single dose doxycycline). In children under eight years, tetracyclines are known to be

associated with teeth discolouration, dental hypoplasia and poor growth of bones. Alternative agents recommended for this age group include azithromycin and ciprofloxacin as was used for our patient (4).

Non-O1 and non-O139 *V. cholerae*, also referred to as non-toxigenic *V. cholerae* are also found in the same environments and are equally pathogenic despite being unable to produce the cholera toxin. They are capable of causing syndromes ranging from mild diarrhoeal illness to invasive diseases like septicaemia and meningitis (5). The source of our patient's infection remains unclear, though the bore water on the family's property is a potential and concerning source.

Invasive infection with non-toxigenic *V. cholerae* is well documented in immunocompromised adult patients as well as those with hepatic disease (3). A retrospective case series of Australian cases from 2000-2013 revealed six episodes of confirmed non-toxigenic *V. cholerae* bacteraemia in adult patients (5). Three of the six patients were suffering from malignancies and two had chronic liver disease. Bore water was suspected to be the source of infection in at least one case (6).

Only seven other documented cases worldwide of neonatal septicaemia as a result of non-toxigenic *V. cholerae* have been published as of June 2020 (1). Interestingly, the majority of

previous cases did not have prodromal diarrhoeal symptoms as our patient did, and all but one were associated with meningitis. There is limited data regarding non-invasive, toxigenic (ie. diarrhoeal) cholera in the newborn and neonatal age group. In endemic areas, children under five years old are disproportionately more affected by diarrhoeal cholera, representing about half of overall cases and deaths. Globally, it is estimated there are at least 11 million cases of diarrhoeal cholera in children under five years annually (2).

The pathogenic mechanisms utilised by invasive non-toxigenic *V. cholerae* remain poorly understood. It is evident in our case that progression of the disease is rapid with pathological changes evident on CT only two to three hours after the onset of neurological symptoms.

The incidence of cholera, regardless of strain varies seasonally with peaks coinciding with warmer temperatures, usually following rainy seasons in tropical areas (8). In the past two decades, there has been increasing awareness and research into the effects of climate change and the warming of sea temperatures. There is mounting evidence that climate change is a driving factor in the spread of bacterial waterborne infectious diseases (9). There have been recent reports of documented outbreaks of *Vibrio* infections in areas with temperate climates including in places with no previous documented incidence of infection (10).

Our patient lived on a cattle farm in northern Victoria, Australia, an area with a cold semi-arid climate. To our knowledge there has not been any documented historical cases of cholera outbreaks in the region. The source of infection still remains unclear, though bore water has been raised as a likely source given the patient's exposure to it and his siblings developing diarrhoea after being exposed. The potential presence of *V. cholerae* in bore water or any other environmental water source in a typically cold climate is of serious public health concern and further investigation is required to explore the relationship to climate change.

While rare, non-toxigenic *V. cholerae* remains an important and potentially lethal cause of meningoencephalitis in newborns. This is the first case of invasive non-toxigenic *V. cholerae* in a newborn reported in Australia. While the source of infection remains unclear, the implications of an environmental source have potentially profound consequences to public health and climate policy.

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Figure Legends

Figure 1. Computed tomography (CT) of the brain on the day of presentation.

Figure 2. T2-weighted magnetic resonance image (MRI) of the brain on day two of admission

Figure 3. T2-weighted MRI of the brain on day ten of admission

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JPC_15063_Figure 1 CTB.png

JPC_15063_Figure 2 MRI T2 Transverse.jpg

JPC_15063_Figure 3 D10 MRI T2 Transverse.jpg

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