

Vibrio vulnificus Infections: Case Reports and Literature Review

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Abstract

Vibrio vulnificus is an emerging opportunistic pathogen that is responsible for one of the most fulminant food-borne diseases in immunocompromised hosts. The infection should be suspected in patients with underlying liver disorders who present with a prominent skin rash, hypotension and septic parameters especially if they give a history of seafood or shellfish ingestion. Awareness and early recognition of this infection will result in a better outcome for the patient.

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Introduction

Infection with *Vibrio vulnificus* is rare but distinctive. Clinical awareness and recognition are needed for its early diagnosis and treatment. A high index of suspicion is important for recognition of this fulminant, rapidly progressive and fatal illness.

V. vulnificus is a ubiquitous gram-negative bacillus that forms part of the marine flora. It is a halophilic (salt-loving) bacteria that thrives during the summer months because it prefers warm sea water which is of more than 20°C. These bacteria are free living but are particularly concentrated in filter feeders like the oysters. Oysters are often implicated as the vehicle of transmission to humans although crabs and eels are also known to harbour these organisms.

This infection represents one of the most fulminant food-borne diseases known to mankind, manifesting as an acute systemic illness without prior gastroenteritis in most cases. Infection is usually contracted through consumption of contaminated shellfish. It presents as a severe sepsis syndrome often with multi-organ failure characterised by fulminant metastatic myonecrosis. Infection is almost exclusively seen in those with liver diseases; especially those that are associated with alcoholism or iron overload like haemochromatosis and

thalassaemia. Mortality is reported to be around 50% but may be as high as 90% in those who have hypotension within 12 hours of admission.*

Another way of acquiring the infection, which occurs in otherwise healthy people, is via contamination of existing skin wounds or fresh injuries with warm seawater. This presents with intense cellulitis and necrotising vasculitis with ulcer formation and gangrene at the initial wound site. Infection may be associated with secondary bacteraemia. Mortality is around 24% with death being mainly seen in those who are immunocompromised with liver diseases.'

A minority may just have gastroenteritis without septicemia or wound infection. This group belongs to those who are immunocompetent and death has not been reported. This distinctive infection has also been recognised in Singapore in the past, being first reported in 1985.² In this review, we report three classical cases of this infection followed by a literature review on the microbiology, pathogenesis, clinical syndromes and management of this rare but fatal infection. It is hoped that this review will alert others to the early diagnosis and management of this fatal infection in future.

Literature review was done through Medline for the period 1984 to 1996 and secondary references. A large

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proportion were single case reports³⁻⁷ with the largest series comprising 62 patients collected by the Florida Department of Health and Rehabilitation Services between 1981 and 1987; from 1981 to 1992, 125 cases were collected in this state.⁸ This infection is now the main cause of fatality from food-borne diseases in Florida. A larger group of patients were also reported from Taiwan, a country where hepatitis B virus infection and cirrhosis are relatively more prevalent.⁹

Case Reports

Case 1

A 42-year-old male lorry driver, with no past history of note, presented to the medical service with a history of fever for three days without chills or rigors. He noted redness and pain over his left calf three days before. It had also become increasingly painful and swollen. There was no history of trauma. He had two episodes of diarrhoea on the day of admission. He smoked 20 sticks of cigarettes and consumed half a bottle of Chinese wine daily since his teenage days.

Clinically, he had a fever of 39.5°C, blood pressure (BP) was 80/50 mmHg on admission which responded to infusion of Hartman's solution. He was noted to be jaundiced with hepatomegaly that was associated with a bruit. His left lower limb was oedematous with overlying bullae. There were also discoloration and ecchymosis. He was given intravenous (iv) ampicillin and gentamicin on admission. This was changed to iv cloxacillin and gentamicin the next day.

Investigations were as follows: haemoglobin 13.4 g/dl, white cell count $6.1 \times 10^9/l$ with polymorphs 87%, platelets $125\,000 \times 10^9/l$, prothrombin time 11 sec (control 11), partial thromboplastin time 36 sec (control 30), D-dimer $<0.5 \mu g/l$. Liver function tests: total protein 49 g/l, albumin 25 g/l, bilirubin $167 \mu mol/l$, alkaline phosphatase 467 u/l, alanine aminotransferase (GPT) 235 u/l, aspartate aminotransferase (GOT) 408 u/l. Chest X-ray was normal. Ultrasound was done first. Ultrasound and computed tomographic scan of the abdomen showed features consistent with early liver cirrhosis.

His fever settled the next day after admission but on the fourth hospital day he became febrile again, went into shock (systolic BP 70 mmHg) and disseminated intravascular coagulation with prolonged prothrombin time/partial thromboplastin time and thrombocytopenia of only $11\,000 \times 10^9/l$. His blood culture was reported to have gram-negative bacilli. He was then transferred to the medical intensive care unit (MICU). Haemorrhagic lesions were noted in his left leg up to his knees with oedema up to his mid-hip. Provisional diagnosis then was gram-negative septicaemia with septic shock and vasculopathy of left lower limb. The aetiology of his peculiar left limb lesions could not be elucidated at that time. Ultrasound doppler of this limb showed no evi-

dence of deep venous thrombosis. Blood culture report returned the next day as *V. vulnificus*. Stool culture was negative.

The patient received iv ceftriaxone and gentamicin for 11 days with aggressive supportive management in the MICU. His fever responded to treatment and his general condition improved. However, the lesions on his left lower limb became ulcerative on the tenth hospital day and then gangrenous within the next 24 hours. Wound culture grew methicillin-resistant *Staphylococcus aureus* as well as multi-resistant *Acinetobacter baumannii* and *Klebsiella* species sensitive to imipenem only. The orthopaedic and plastic surgeons were called in to co-manage the case. The patient received multiple repeated desloughing with appropriate antibiotics cover for the multi-resistant bacteria. He finally received a skin graft and was discharged well.

Case 2

A 61-year-old fishmonger had complained of fever for one day accompanied by vomiting and lethargy. She went to see a general practitioner who prescribed some symptomatic treatment. On the same day she developed patches of red painful rashes which she described as "bruise-like" on her abdomen and arms. She fainted in the toilet on the same night and was brought to the hospital. At the Accident and Emergency Department she was hypotensive with a BP of 74/33 mmHg. She had a history of hypertension on nifedipine and atenolol.

In view of her peculiar rash (Fig. 1), she was referred to the Infectious Disease physician on the following day of admission. She had multiple tender discrete erythematous annular rash on her torso and shoulder (Fig. 2). Some of them had evolved with central areas of pallor resembling the lesions of erythema multiforme (Fig. 3) while some were bullous lesions (Fig. 4). They became gangrenous and necrotic the next day. This rash with the typical evolution was most characteristic of *V. vulnificus* septicaemia. Blood culture on the second day of admission grew gram-negative bacilli.

A diagnosis of *V. vulnificus* septicaemia was made. History retaken from the patient's son revealed that the patient was a hepatitis B virus carrier but had no history of liver disorder. The patient had also consumed crabs about two weeks before admission. The patient denied any pre-existing wounds or fresh injuries during the course of her work as a fishmonger.

The patient was ill on admission to the ICU. She was diagnosed with disseminated intravascular coagulation (DIC), renal impairment and early liver decompensation. Supportive management was implemented and she was started on iv ceftazidime and oral doxycycline. She improved initially but subsequently went into nosocomial sepsis with multi-organ failure.

Her course of illness was complicated by liver failure



Fig. 1. Denuded bullae and annular erythematous rash in Case 2

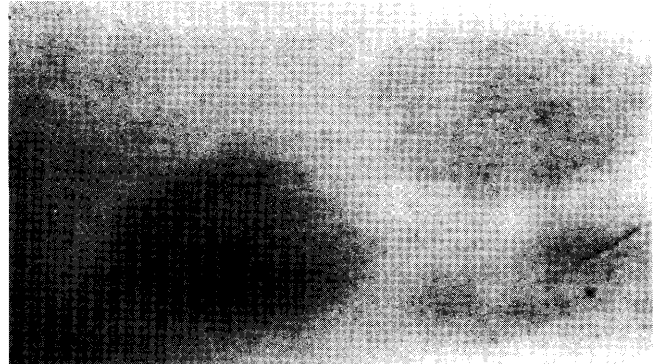


Fig. 2. Multiple discrete erythematous annular rash in Case 2.

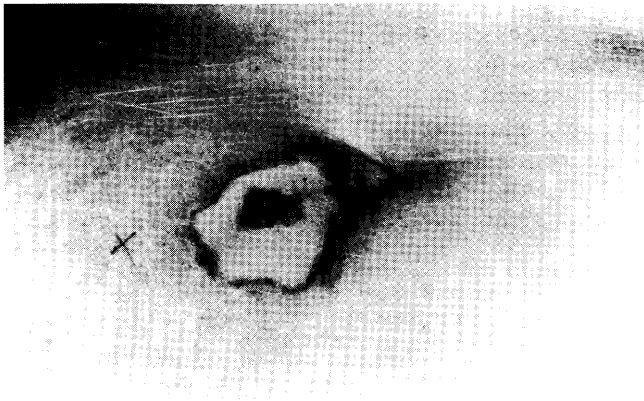


Fig. 3. Some of the lesions in Case 2 resembling erythema multiforme.

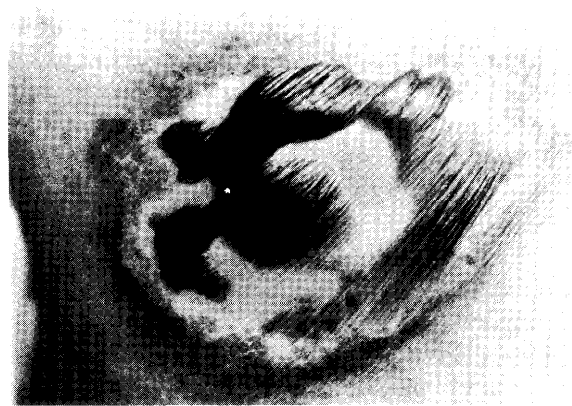


Fig. 4. Bulbous lesions seen in Case 2

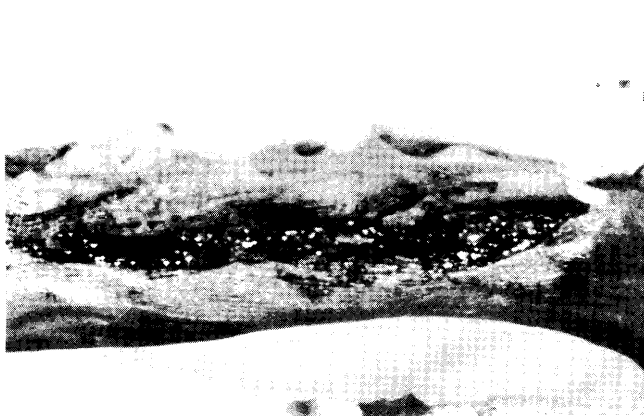


Fig. 5. Exposed wound of Case 3 showing extensive myonecrosis with bone exposed.

and doxycycline was stopped. New lesions with severe wound necrosis at multiple sites formed despite being on antibiotics. These were colonised with various multi-resistant organisms. Debridement of her wounds was limited by her abnormal coagulation profile and thrombocytopenia. She developed bacteraemia with multi-resistant gram-negative organisms from the colonised sores. She was given appropriate antibiotics but developed allergic reactions to imipenem and ciprofloxacin; hence, limiting our antibiotic choices. She subsequently

went into renal failure and collapsed and died after seven weeks of hospitalisation.

Case 3

A retired 62-year-old male, formerly a taxi driver, was admitted to the Medical Department after presenting at the Emergency Department with a 3-day history of fever, chills and rigors associated with a painful and swollen right heel. There was no history of trauma to the heel. He had 2 episodes of loose stools on the day of admission. He was a chronic heavy smoker and ethanol abuser, consuming 3 large bottles of beer daily for the past 18 years. He had pulmonary tuberculosis treated 5 years ago. There was no history of liver disease.

At the Emergency Department, he had a temperature of 38.4°C. BP was 100/60 mmHg. This dropped to 85 mmHg systolic in the ward. His right heel and the lower end of his shin were swollen with haemorrhagic blisters. He was diagnosed to have cellulitis and was started on iv ampicillin and cloxacillin. The next day, his right toes became gangrenous with proximal extension of the rash. On the third day of admission, he went into septic shock with disseminated intravascular coagulation and was sent to the MICU. The antibiotics were changed to iv crystalline penicillin and ampicillin-sulbactam.

Investigations: haemoglobin 11.2 g/dl, white cell count $14.9 \times 10^9/l$, polys 90%, platelets $51\,000 \times 10^9/l$. Prothrombin time 28.7 sec (control 12), partial thromboplastin time 45.8 sec (control 27.1). D-dimer 1.5 ul/g. Liver function tests: total protein 54 g/l, albumin 24 g/l, bilirubin 27 $\mu\text{mol/l}$, serum alkaline 233 u/l, alanine aminotransferase 67 u/l, aspartate aminotransferase 45 u/l.

The patient was seen by the Infectious Disease Service on the third day of admission. He was noted to have stigmata of chronic liver disease viz. palmar erythema, clubbing and ascites. The typical rash of haemorrhagic blisters with rapid progression to peripheral gangrene was immediately recognised. The patient was asked for a history of seafood ingestion and seawater exposure. He admitted to consumption of lightly steamed cockles about two weeks before admission. Infection with *V. vulnificus* was diagnosed. iv ceftazidime 1 g 8 hourly and oral doxycycline 100 mg 12 hourly were started while awaiting blood culture results.

His blood culture was reported to have gram-negative bacilli later that day; the laboratory staff was alerted to possible *V. vulnificus* infection. This was confirmed the next day. The bacteria were resistant to ampicillin, gentamicin and cephalothin but sensitive to third-generation cephalosporins and tetracycline. He remained stable but his rash progressed with extensive necrosis and gangrene; he was given a generous debridement. There was severe myonecrosis with the bone exposed after the debridement (Fig. 5). Tissue culture taken during the operation was positive for *V. vulnificus*. Unfortunately, a similar rash appeared on the corresponding area of the other leg a day later. In addition; his wound on the right side grew multi-resistant *Stenotrophomonas maltophilia* that was sensitive to chloramphenicol only. The surgeon decided to go ahead with an above-knee amputation as the limb was deemed unsalvageable. He was started on iv chloramphenicol 500 mg six hourly preoperatively. The left lower limb was also debrided.

Ultrasound examination of the abdomen showed a cirrhotic liver with ascites and hepatosplenomegaly. Hepatitis A and C virus serologies were negative. He was immune to hepatitis B virus (anti-HBsAb >150 MIU/M). Stool culture was also negative.

Postoperatively, the patient was continued on iv ceftazidime, chloramphenicol and oral doxycycline. His BP normalised without inotropes and coagulation profile (PT, PTT) became normal. He made a progressive recovery and was discharged well from the hospital.

Discussion

Microbiology

V. vulnificus is a recently discovered bacteria that is being increasingly recognised as an opportunistic patho-

gen.⁹ This rod-shaped, slightly curved motile bacillus was first isolated in 1976 by Hollis et al¹⁰ who described it as a *Vibrio* species distinct from other halophilic (salt-loving) *Vibrios* viz. *V. parahaemolyticus* and *V. alginolyticus* because of its predilection for extraintestinal sites and a different biochemical profile. *V. vulnificus* has a lower salt tolerance and the ability to ferment lactose and produce beta-galactosidase. This bacterium was more often cultured from tissue and blood than from stool samples. The clinical syndrome associated with this organism was first described in 1979.¹¹ It was in the same year that this organism was renamed *V. vulnificus*, previously known as *Beneckea vulnifica*.

V. vulnificus is a ubiquitous gram-negative bacillus that thrives in warm marine water of more than 20°C. It grows readily on ordinary 5% blood agar after overnight incubation and appears as smooth opaque colonies of about 2 mm in diameter. Non-pathogenic strains were noted to form translucent colonies.^{12,13} Prolonged incubation of up to 48 hours will reveal a clear zone of haemolysis around the colonies with a greenish discoloration of blood cells in the area of confluent growth. Locally, we have had no difficulty identifying this rare organism which can be confused with other gram-negatives like *V. parahaemolyticus*, *Pseudomonas* species, *Aeromonas hydrophila*, *Plesiomonas shigelloides* and *Serratia marcescens*. *V. parahaemolyticus* and *alginolyticus* do give rise to systemic infections viz. soft tissue infections and otitis media but they are rare and mostly non-fatal. Previous episodes of fatal septicaemia before 1979 are now believed to be due to the lactase-positive *Vibrio* (*V. vulnificus*) instead.⁴

Epidemiology

Infections with *V. vulnificus* are rare and sporadic. True incidence of infection is not known. In a regional surveillance involving four states along the gulf coast of the USA, annual incidence was estimated at 0.6 per one million persons with a case fatality of 22%.⁸ In one large study in Florida,⁸ it was estimated that adults with liver disease are 80 times more likely to suffer from infection and 200 times more likely to die from the infection after consumption of raw oysters compared to adults without underlying liver diseases. The incidence of infection for this special group was estimated to be 72 per 1 million adults.⁸

Singapore boasts of the largest per capita consumption of seafood in the world. It is a tropical island surrounded by warm seawater. These two factors make us particularly vulnerable to acquiring *V. vulnificus* infections. However, with the exception of cholera, other *Vibrio* diseases are not notifiable in Singapore and we do not know the true incidence of this infection.

Halophilic marine *Vibrios* are the most common bacteria found in marine waters where they account for 31.2%

of all bacteria isolated.¹⁴ Besides being naturally found in the water, they are especially concentrated in filter feeders like oysters and other shellfish. A study from the US East Coast waters found oysters and clams constituted 84% of the isolates found in animals.¹⁵ Oysters were the commonest shellfish implicated in clinical cases studied⁸ though crabs,¹⁶ prawns, eels¹⁷ and fish were known to harbour this organism; giving rise to clinical infections. Analysis of exposure histories in one study¹⁸ revealed 89% of patients developing primary septicæmia had eaten raw oysters within two weeks before the illness compared to only 26% of matched controls who had also eaten raw oysters within the same period ($P < 0.01$). This was again validated in the largest series involving 125 persons where 58 out of 72 persons (81%) with primary septicæmia gave a history of raw oysters consumption during the week before the onset of illness.⁸

Ingestion of as few as three oysters was known to cause infection but no correlation was seen between the number of oysters consumed with either the incubation period or the case-fatality rate.¹ The bacteria is easily killed by cooking; their viability also decreases proportionately with the duration of refrigeration.¹⁴

Ingestion of raw or partially cooked seafood is thus one of the portals where the bacteria gain entry into our body. This route of infection is associated with primary septicæmia. The incubation period cited in different papers varies; in the earliest study¹ it was reported to be from 7 hours to one day (median 16 hours). In another study,¹ the majority (25 out of 39 cases) presented within 24 hours with a median of 18 hours.

All our three cases gave a distinct history of seafood ingestion. Case 1 took "yu sheng" or raw fish, Case 2 had taken crabs and Case 3 took steamed cockles. The incubation period of about two weeks (Cases 2 and 3) was rather long compared to other case studies, Incubation periods for as long as two weeks had been reported before.¹⁴ With only 3 patients, we could not conclude that our local patients have a longer incubation period. It is not known whether clinical presentations differ with different incubation periods.

Another route of infection is via the skin. Existing wounds, cuts or abrasions when contaminated with marine water, serve as portals of entry. The bacteria may also gain entry as a result of cuts from rocks, bites from crabs, puncture wounds from shrimps or fish barbs, insect bites on skin contaminated with sea water or cuts from knives that were used to prepare contaminated seafood.¹⁷ Case reports of these various routes of entry had been reported.^{14,18} It is interesting that the patient in Case 2 was a fishmonger because infection through wounds or injuries will definitely pose as an occupational hazard. Repeat questioning, however, failed to reveal such a portal of entry for this patient. Infection

through this route ranges from mild cellulitis to fulminant wound infection with gangrene, often with secondary bacteraemia.

Most cases, up to 100% in one series,⁹ occurred during summer or early fall. It is at this time that the bacteria are most abundant as it thrives in warm water. This is also the time when recreational contact with marine water is the greatest.

Who are at risk of infection? The infection is rare despite the fact that the organism is ubiquitous and consumption of raw seafood is widespread. Epidemiology had shown a strong correlation between the primary septicæmic form with chronic underlying medical conditions.¹⁸ In the series by Howard and Bennett,¹⁴ 39 out of 49 patients with primary septicæmia had severe liver disease and cirrhosis, the other 10 had other medical conditions viz. cancer, diabetes mellitus, steroid use and previous gastric surgery. In the series by Klontz et al,¹ liver disease occurred in 25 out of 38 patients (66%; 95% CI: 50 to 82); 12 patients had alcoholic liver disease, five had haemochromatosis and eight had liver disease of unknown cause. Similar associations were seen in other large series.^{9,19}

In contrast to the primary septicæmic form, primary wound infections with or without secondary bacteraemia appear to involve immunocompetent hosts although mortality is noted to be higher in those with the underlying disorders mentioned above.⁷

This strong association with liver disease is seen in all our three cases. Case 1 had early liver cirrhosis from alcoholism, Case 2 was a known hepatitis B virus carrier and Case 3 had decompensated alcoholic liver disease. Case 2 could have had subclinical liver disease although she had no prior liver function test available to confirm our suspicion. It is not known whether those few reported cases involving seemingly immunocompetent hosts had actually subclinical liver disorders. Case 2 also illustrated another point of interest; she had gone into acute hepatic failure with encephalopathy during the course of her illness. Whether the infection precipitated the liver failure is unclear as this complication was not mentioned in all the large series reviewed, except for one case report which involved septicæmia with two organisms viz. *V. vulnificus* and *Clostridium bifermentans*.²⁰

Infections with *V. vulnificus* involve both the young (especially those with thalassaemia) and the elderly in whom chronic disorders are more prevalent. All studies showed a male predominance. This could be explained by the fact that alcohol-related liver disease and outdoor activities are more prevalent in male patients.

Pathogenesis

The susceptibility of patients with underlying liver disorders to infection has been linked to the utilisation of

the host's iron stores.^{12,21} The bacteria is exquisitely sensitive to iron which serves as a nutrient for its growth. The administration of iron to experimental animal host had been shown to significantly decrease the infectious dose needed for clinical infection. For maximum utilisation of iron by the bacteria, transferrin has to be at least 30% saturated with iron. On the other hand, there is no evidence of association between increased pathogenicity and serum ferritin levels, suggesting that transferrin saturation is the important variable. It is for this reason that patients with haemochromatosis and thalassaemia are especially susceptible to this microbe. Not only is the inoculum for infection lower, the illness is uniformly fatal in those with haemochromatosis.^{9,11} Alcohol may also increase iron absorption in the form of ferric ions by stimulating gastric acid secretion. Chronic liver disease is associated with decreased protein synthesis including transferrin suggesting that cirrhotics may have increased levels of free iron available for utilisation by the pathogen. Alcoholics, especially those with accompanying cirrhosis, form another group of susceptible victims. Males also have higher saturated transferrin levels; another reason why males are more commonly affected. In cirrhotics with portal hypertension, bacteria can totally bypass the protective reticuloendothelial system of the liver as a result of blood shunting. It is also believed that cirrhosis promotes leakage or translocation of bacteria across the gut wall to the blood stream via the lymph nodes. Finally, alcoholism, like other chronic illnesses viz. diabetes mellitus, renal failure or steroid use, is associated with depressed immunity, particularly defective opsonisation and intracellular killing from neutrophils and macrophages. The presence and type of bacterial capsule are associated with virulence. The capsule confers protection by resisting phagocytosis by the host cell.²¹ Only encapsulated ones are pathogenic and for unknown reasons, the bacteria is capable of shifting from unencapsulated to encapsulated phenotypes. Among the encapsulated, only certain capsular types are associated with clinical disease.²² It is estimated that less than one per cent of environmental isolates actually belong to the virulent group.²³ Therefore, the combination of a susceptible host and a virulent strain is needed for infection to occur. This explains the infrequent occurrence of this unique infection.

V. vulnificus elaborates a range of extracellular cytotoxins²⁴ viz. haemolysin, proteases, lipases, mucinase, DNAase, collagenase and various phospholipases. These cytotoxins are responsible for the extensive tissue destruction seen. It is not clear why this organism has a profound propensity to seed soft tissue and skeletal muscles sparing the internal organs since bacteraemic spread is believed to be the underlying mechanism of invasion. Injection of the bacteria into animals causes swelling with oedema at the site of inoculation explain-

ing the accompanying oedema of the affected limbs that is often reported.²⁵ This tense oedema together with vasculitis compromise the blood supply to the affected areas accounting for the rapid progression of the wound and peripheries to gangrene. For the same reasons above, antibiotics will have poor penetration to the affected areas. The rash, therefore, usually progresses despite appropriate antibiotic therapy emphasising the need for early and aggressive surgical intervention.

Histology of the lesions usually reveals acute necrotising inflammation of skin and soft tissue described as cellulitis, vasculitis, panniculitis and fasciitis.²⁰ The organism may also be seen on histology or culture from the bulla fluid or soft tissue.^{1,19} In Case 2, the culture of the bulla fluid was negative but this was taken after antibiotics were started. Culture of debrided tissue in Case 3 was, however, positive for the bacteria.

Clinical Syndromes

Two main clinical entities have been well described. They are the primary septicaemic form and primary wound infection with or without septicaemia. Some series described gastroenteritis as the third clinical entity.^{1,9,14} There were also isolated case reports of rare presentations. Such cases include a young man with thalassaemia who developed acute epiglottitis secondary to oral exposure to contaminated fish tank water,²⁶ two cases with corneal ulcers,²⁷ two cases of pneumonia seen after near drowning^{9,28} and a boy with thalassaemia with meningitis after raw oyster ingestion.²⁹

Primary septicaemia: Primary septicaemia occurs almost exclusively in those who are immunocompromised in one way or another. Illness begins abruptly with fever and chills without any apparent source of sepsis. There may be accompanying mental changes. A third of patients may be in shock either at the time of hospital admission or within 24 hours of admission.¹⁹ Most impressive are the typical skin lesions which developed in about three-quarters of the patients.^{1,19,23}

Skin lesions are usually present at the time of admission or often appear within 24 hours of the infection. Most of the lesions were said to occur at the peripheries (Cases 1 and 3)¹⁴ but they may also be present on the trunk (Case 2).¹⁹ These lesions usually progress in the manner that was classically seen in Case 2. New lesions may also develop while the patient is on antibiotics. In many instances, there is a maculopapular or annular erythematous rash which may then become bullous or ecchymotic, progressing to necrotic ulcers and gangrene.

The rash is distinctive and the infection should be recognised in any acutely ill patient with underlying liver disease and recent ingestion of seafood. We are aware that food history may not be asked in routine

medical history taking. In both of our two recent cases, the diagnosis was made before the blood cultures were back. In Case 2, we retook the history and interestingly found that the patient was in fact a hepatitis B virus carrier with a history of recent crab ingestion. In Case 3, although he had no history of liver disease, he gave a history of ethanol abuse and had obvious stigmata of chronic liver disease clinically. We made our diagnosis from the clinical presentation, the rapid progression of the typical rash and the fact he had underlying decompensated alcoholic liver disease. When asked specifically for a history of seafood ingestion, he gave a positive response. This emphasised the need to be able to recognise the rash, in order to obtain a history of risk factors.

All the series quoted reported a mortality of around 50%; this rose to 90% in those who had hypotension within 12 hours of admission. Hypotension was the single most important prognostic variable.¹ Most deaths occurred within 48 hours of admission.^{7,9,14} Patients are extremely prone to nosocomial infection resulting from colonisation of the multiple skin lesions with multi-resistant gram-negative bacteria and methicillin-resistant *S. aureus* as seen in all our cases here. Early debridement or amputation should be considered when tissue compromise is extensive or if antibiotics cannot control the spread of infection. Surgical procedures are often hampered by abnormal coagulation profile and thrombocytopenia secondary to the sepsis or underlying liver disease. It is most unfortunate that Case 2 ultimately succumbed to nosocomial bacterial sepsis from the secondarily infected wounds. All these factors add to the high mortality of this infection.

Wound Infections: Wound infections may be mild and self-limiting or progress rapidly and relentlessly to bullae formation, skin necrosis, necrotising fasciitis or rhabdomyolysis,^{5,30} often mimicking gas gangrene. As mentioned earlier, infection occurs in both immunocompetent and immunocompromised hosts but death from this mode of presentation usually occurs in the latter group. In the series from Taiwan,⁸ the mortality was 25.3% for wound infection compared to 54.2% in those with primary septicaemia. A similar condition may be seen with infection from *Aeromonas* species but this usually results from contamination of wounds with fresh water. Infection with *Aeromonas* is also seen mainly in immunocompromised patients although this is not exclusive.³¹

Gastroenteritis: This refers to infection of the gut without any extraintestinal manifestations. Seventeen per cent to 40% of the septicaemic form may also have diarrhoea or vomiting at presentation; however, it seldom presents as a problem.^{11,18} This entity is rather uncommon compared to the above two categories, perhaps due to under-reporting, since the disease is usually mild and therefore not brought to medical attention. It

has not been associated with any death so far. Patients usually present with watery to bloody stools associated with vomiting and abdominal cramps. Symptoms may last for more than a week. Use of antacids or cimetidine resulting in decreased gastric acidity may be a risk factor.³² All stool specimens were positive for the three cases reported by Johnston et al.³² Stool culture may be positive or negative in those who have primary septicaemia with diarrhoea. It may also be positive in those without diarrhoea implicating the gut as a source of entry in patients with primary septicaemia.^{1,19}

Antibiotics therapy: Unfortunately, there are no adequate clinical data on antibiotic efficacy to support fully any recommendation for this potentially life-threatening infection. There have been no controlled drug trials of this rare infection to this day.

Aggressive early treatment with antibiotics is advised as delay is associated with increased mortality.* Although the sensitivity tests often show the organism to be susceptible to a wide range of antibiotics including ampicillin, cephalothin, chloramphenicol, tetracycline and gentamicin; the *in-vitro* activity of some of these drugs may not correlate well with *in-vivo* efficacy as illustrated by the experience with cholera. Use of gentamicin is also debatable. Very high doses are suggested for it to be efficacious.²⁵ Tetracycline was recommended as the drug of choice in some series but the superiority of tetracycline was based on *in-vitro* sensitivity and animal studies.²⁵ Successful treatment had been reported in patients given chloramphenicol,²⁹ third generation cephalosporins⁹ and tetracycline.⁷ Dual antibiotic therapy is recommended for this life-threatening infection.

Suggested combinations include tetracycline with gentamicin^{23,25} or a third generation cephalosporin with tetracycline.^{9,14}

We have chosen a third-generation cephalosporin and doxycycline for our patients although it is not clear whether results from tetracycline could be extrapolated to doxycycline. It should also be realised that doxycycline is potentially hepatotoxic and caution should be exercised in its usage particularly in those patients who may already have an underlying liver disorder.

Conclusion

Finally the authors would like to reiterate two points. Firstly, in view of the extremely high mortality rate associated with *V. vulnificus* septicaemia despite the institution of appropriate antibiotics, efforts should be directed towards prevention. It is the responsibility of the physicians to educate patients who are immunocompromised to eat their seafood well-cooked or to abstain from them totally. Patients with various liver disorders should not just be told to avoid alcohol but also to abstain from raw or partially-cooked seafood. Exposure of wounds to seawater should be discouraged.

Persons handling shellfish should wear thick rubber gloves to minimise the risk of puncture wounds.

Raw shellfish may also carry other pathogens like the hepatitis A virus and Norwalk viruses, *Salmonella*, other *Vibrios* and *Campylobacter* species, not to mention the potential of paralytic shellfish poisoning from toxic dinoflagellates. Hence, avoiding raw or partially-cooked shellfish will also prevent infections with these other organisms.

Secondly, this article is intended to create awareness among our colleagues of this rare but fatal infection that is readily recognisable with its distinctive clinical presentation. We anticipate that there will be more of such cases in the future. Such cases may present to either the medical or orthopaedics wards. A high index of suspicion for this unusual infection will bring about early institution of appropriate antibiotics and intervention resulting in a better outcome.

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