Severe necrotising fasciitis of the extremities caused by Vibrionaceae: experience of a Hong Kong tertiary hospital

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Necrotising fasciitis is an uncommon soft tissue infection characterised by the widespread necrosis of subcutaneous tissue and fascia, and secondary necrosis of the overlying skin. Ten patients who had necrotising fasciitis were admitted to the intensive care unit at the Prince of Wales Hospital between June 1994 and August 1997. The necrosis in six patients was caused by marine Vibrionaceae. Because of the rapid onset of necrosis, progression to severe disease, and frequently fatal outcome, the public (especially at-risk individuals), general practitioners, and specialist medical personnel should be made aware of the clinical syndrome of necrotising fasciitis caused by marine Vibrionaceae. The diagnosis is dependent on a high index of suspicion, which should be aroused by the presentation of an immunocompromised patient with an extremity lesion and a history of contact with raw seafood or a warm aquatic environment. Once the disease is suspected, treatment should be a course of a third generation cephalosporin, and fluoroquinolone or tetracycline. Aggressive surgical debridement is recommended.

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Introduction

Necrotising fasciitis is an uncommon soft tissue infection characterised by the progressive inflammation and necrosis of soft tissue that spread to subcutaneous tissue and fascia, causing secondary necrosis of the overlying skin and muscle.[1,2] The disease is usually associated with systemic toxicity and has a high morbidity and mortality rate despite the use of antibiotics, intensive care management, and advances in surgical technique.[1,2] There has recently been a substantial increase in the recognition and reporting of necrotising fasciitis, and much attention has been given to the most common causative organism worldwide—S*treptococcus pyogenes* (Lancefield group A).[1,2,3] Severe necrotising fasciitis is frequently associated with septic shock; affected patients require treatment in an intensive care unit (ICU) if they are to survive.

We retrospectively identified 10 cases of necrotising fasciitis from the admission records of the ICU of the Prince of Wales Hospital from June 1994 to August 1997. The majority of cases were caused by organisms other than group A streptococci and six were caused by marine Vibrionaceae. Microbiology records corresponding to the review period were retrospectively examined to establish the frequency of positive cultures of Vibrionaceae that were capable of causing necrotising fasciitis. The epidemiology, presentation, and treatment of severe necrotising fasciitis caused by Vibrionaceae are reviewed.

Case reports

A summary of the clinical features of the patients who were admitted to the Prince of Wales Hospital from June 1994 to August 1997 with necrotising fasciitis caused by Vibrionaceae is shown in Table 1. The presentation of all six cases of necrotising fasciitis was similar. All patients presented with a primary complaint of swelling and tenderness of an extremity

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associated with the abrupt onset of symptoms of sepsis—malaise and rigors. Cutaneous lesions, usually erythematous areas overlying the tender swelling, were present in all patients. Four of the six patients were afebrile on presentation. All six, however, became febrile within 12 hours of admission to hospital; within 24 hours of admission, all patients met the criteria for septic shock (defined as showing clinical evidence of acute infection and at least three of the following: temperature >38.3°C; pulse rate >90 beats per minute; tachypnoea >20 breaths per minute; white blood cell count >$12x10^9$/L; and systolic blood pressure <90 mm Hg or the requirement for inotrope infusion to maintain this pressure). The rapid systemic deterioration was accompanied by the equally rapid local progression of swelling and the appearance of bullous skin lesions in all patients (Fig).

Single organ dysfunction occurred from the first day of admission in all patients. Failing organ function was supported by using standard ICU protocols, which included invasive monitoring, fluid therapy, use of inotropes and vasopressors, ventilation, and continuous veno-venous haemodiafiltration. Despite aggressive therapy, there was rapid progression to multiple organ failure and a high mortality rate. The antibiotic treatment, surgical management, and treatment outcome are summarised in Table 2. The only survivor (patient 4) was the only patient to present for treatment at an early stage of disease (within 24 hours of the onset of symptoms) and thereby immediately receive both aggressive surgery and appropriate antibiotic therapy.

A retrospective microbiological review of the Prince of Wales Hospital identified only five in-patients from whom *Vibrio vulnificus* was isolated over the 3-year review period. All five patients were admitted to the ICU and were included in this study. As it is relatively easy to culture *V vulnificus* from human specimens, it is unlikely that less severe cases of infection were overlooked in the hospital wards. In contrast, *Aeromonas hydrophila* was isolated from 21 ward patients (one of whom was from the series of patients admitted to the ICU) during the same period. These findings suggest that *V vulnificus* causes a more severe infection than *A hydrophila* and that the illness resulting from *V vulnificus* infection has a more fulminant course. Five of six Vibrionaceae infections occurred during the summer months and all patients resided in Hong Kong. Recent exposure to seafood and/or seawater was documented by four of the six patients. Only one patient developed gastro-intestinal disease (manifested by diarrhoea) that was known to be associated with Vibrionaceae. The stool culture from this patient was negative for *V vulnificus.*

Table 1. Characteristics of six patients with severe necrotising fasciitis caused by Vibrionaceae

Patient	Age/sex (years)	Date of onset of symptoms	Exposure	Chronic disease	Symptom duration before hospital admission
1	54/M	Jun 1994	Estuarine and flood waters; no known injury	Alcoholic cirrhosis	2 days
2	64/M	Dec 1994	Minor abrasion; raw shellfish consumed; no water contact	Alcoholic cirrhosis	2 days
3	53/M	May 1995	Ankle sprain 9 days before symptom onset; no water contact	Peptic ulcer	3 days
4	53/M	Jun 1996	No trauma; raw shellfish consumed; no water contact	Chronic atrial fibrillation, gout	1 day
5	72/F	Jul 1996	None	None	1 day
6	66/M	Aug 1997	Minor abrasion from fish falling on foot	Diabetes	3 days

* NF Necrotising fasciitis
† VI Vibrionaceae infection
‡ Cultures from blood and tissues, except for patient 6 (tissue only)

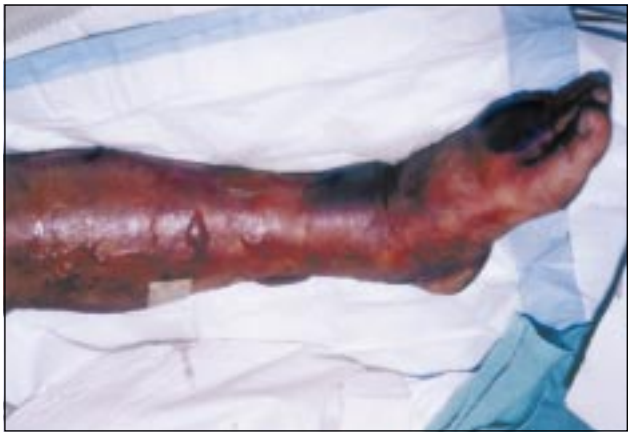

Fig. Photograph showing the violaceous blisters characteristic of *V vulnificus* necrotising fasciitis

Discussion

Vibrio, Aeromonas, and *Plesiomonas* are the three genera of the family Vibrionaceae that have clinical significance in humans.[4] *A hydrophila* is found in fresh water or fresh water/salt water interfaces throughout the world,[5] whereas *V vulnificus* is found in the warmer coastal waters of America, Europe, Asia, and Australia.[6-15] Both *Vibrio* and *Aeromonas* species are associated with three clinical presentations—sepsis with no obvious source of infection, gastro-enteritis, and severe soft tissue infections such as necrotising fasciitis.[5,6] Our findings suggest that while *A hydrophila* infection is more common, it is much less likely than *V vulnificus* to cause severe necrotising fasciitis. Although necrotising fasciitis is rare, the incidence of disease caused by *V vulnificus* appears to be increasing.[7,8] The reason is unclear but may be related to an increase in the awareness of clinicians in high-risk areas, a rise in the popularity of raw seafood, or an increase in the number of susceptible individuals. Patients who are also immunocompromised are more susceptible to disease caused by Vibrionaceae; the patients in our series, and in the majority of case reports, had diabetes or chronic liver disease, or were receiving long-term steroid medication.[6,8] Patients with altered gastric pH (eg with achlorohydria or taking H_2-receptor antagonists) or hyperferraemia (eg haemochromatosis, thalassaemia) are also at risk.[7,16] In addition to being at a higher risk of necrotising fasciitis, patients who are immunocompromised have a poorer prognosis.[16]

Patients who develop soft tissue infections and systemic sepsis frequently become critically ill and require intensive care. Our experience, and that of others, shows that shock and death can occur rapidly; 50% of the patients who die do so in the first 48 hours of disease onset.[6,8] The key to management is early diagnosis based on a high index of suspicion. Symptoms may occur from 24 hours to many days after

Clinical features on first presentation	Gastro-intestinal symptoms	White cell count	Initial diagnosis	Time from admission to diagnosis of NF*/ suspected VI† (hours)	Culture‡
Fever; tender, swollen left foot; ecchymoses; blisters; hypotension	None	$26.5x10^9$ /L	Haemorrhagic rash	6/48	*V vulnificus*
Fever; rigors; tender left foot; ecchymoses; blisters; hypotension	None	$14.4x10^9$ /L	Cellulitis	12/12	*A hydrophila*
Fever; rigors; painful, tender left foot; erythema; ecchymoses; blisters; hypotension	None	$28.4x10^9$ /L	Cellulitis	12/12	*V vulnificus*
Swollen, painful, tender right calf; erythema; malaise	None	$7.9x10^9$ /L	Deep venous thrombosis	24/24	*V vulnificus*
Swollen, painful, tender right calf; diarrhoea; hypotension	Diarrhoea	$10.0x10^9$ /L	Gastro-enteritis	12/12	*V vulnificus*
Fever; rigors; increased pain and tenderness of left foot; erythema; blisters; hypotension	None	$28.6x10^9$ /L	Osteomyelitis	10/10	*V vulnificus*

exposure. The diagnosis should be considered in any patient who has extremity pain and erythema, or who has had recent exposure to raw seafood or a marine environment; necrotising fasciitis should also be part of the differential diagnosis of cellulitis. Necrotising fasciitis should be suspected when limb pain or systemic illness is 'disproportionate' to the skin changes. Computerised tomography and magnetic resonance imaging are useful in locating the site and depth of infection, and study of a frozen-section biopsy, if available, provides relatively fast and specific information.[1] The diagnosis is more likely if bullous cutaneous lesions develop. Once necrotising fasciitis is suspected, cultures of blood, stool, and blister fluid, as well as wound specimens should be taken and aggressive management begun immediately. Gram stains of cultures that display curved bacilli with or without pleomorphic forms should be regarded as suggestive of the presence of *Vibrio* organisms.[16]

Early treatment with appropriate antibiotics may improve outcome.[17] It is important to remember that antimicrobial sensitivities of *Vibrio* organisms (Table 2) are different from those of the group A streptococci. We recommend, based on the 100% in vitro disc sensitivity from this study and from those of others,[8] a third generation cephalosporin such as ceftazidime. As no randomised controlled trials are available, however, definitive recommendations about antibiotic therapy cannot be made. Howard and Bennett[6] recommend that a second antibiotic be given and, based on known in vitro sensitivities and available case reports, a fluoroquinolone such as ciprofloxacin or tetracycline may also be used as a second agent.[6,7,11,17,18] Because of the high frequency of renal failure in our series of patients, we have been reluctant to use either aminoglycosides or tetracycline as part of treatment. However, an animal study has shown that tetracycline may be useful to treat *V vulnificus* infections, as has also been suggested by a report on a human series.[17,18]

We recommend transferring an infected patient to an ICU for close monitoring and aggressive supportive care; this recommendation has been supported by others.[7] The clinical course is one of systemic inflammatory response that rapidly progresses to septic shock, multiple organ dysfunction syndrome, and early death in a high proportion of cases (Table 1).[8] Because of this rapid progression, early and aggressive debridement of wounds (within 72 hours of symptom onset or 24 hours of hospital admission)[8] and amputation, if indicated, are essential components of therapy and may be life-saving.[7,8,10] In one series, early surgery resulted in a decreased ICU and hospital stay.[19] In our experience, where delayed aggressive debridement or amputation leads to septic shock (either because of late presentation or incorrect diagnosis), death is likely to occur despite having used appropriate antibiotics. Close surgical observation with a low threshold for surgical exploration is mandatory. Although *A hydrophila*

Table 2. Disease progress, and treatment outcome

Patient	Septic	Organ failure	Initial antibiotic/s	Antibiotic disc sensitivities of cultured bacteria
1	Y	Encephalopathic*, hepatic†, renal‡, respiratory§, DIC‖	Cephradine	Ampicillin, aminoglycosides, cefuroxime, ceftazidime, cotrimoxazole, tetracycline
2	Y	Encephalopathic, hepatic, renal, respiratory, DIC	Penicillin G, metronidazole	Ampicillin, netilmicin, cefuroxime, ceftazidime, cotrimoxazole, tetracycline
3	Y	Encephalopathic, hepatic, renal, DIC	Penicillin G, metronidazole, cloxacillin	Ampicillin, netilmicin, cefuroxime, ceftazidime, cotrimoxazole,
4	Y	Encephalopathic, hepatic, renal, DIC	Penicillin G, ceftazidime, metronidazole	Ampicillin, aminoglycosides, cefuroxime, ceftazidime, cotrimoxazole, ciprofloxacin
5	Y	Encephalopathic, hepatic, renal, respiratory, DIC	Ampicillin, cloxacillin	Chloramphenicol, cefotaxime, ceftazidime, cotrimoxazole, tetracycline
6	Y	Encephalopathic, hepatic, renal, respiratory, DIC	Penicillin G	Ampicillin, chloramphenicol, cefuroxime, ceftazidime, cotrimoxazole

* Score of <6 on Glasgow coma scale for non-sedated patient
† Bilirubin level >120 μmol/L
‡ Serum creatinine >350 μmol/L or urine output <500 mL/d

infection may involve muscle, *V vulnificus* infection often does not. It is thus important not to underestimate the extent of soft tissue involvement, as complete removal of necrotised fascia and subcutaneous tissue is essential. Healthy muscle may need to be sacrificed by amputation if progression of the disease cannot be halted by debridement.[6]

There has been a steady increase in the number of reports of *V vulnificus* infections from Asia in the past 10 to 15 years.[20] Before 1994, only four cases of *V vulnificus* necrotising fasciitis had been reported from Hong Kong.[12-15] Our experience, although gathered from only one institution, strongly suggests that this increase is occurring in Hong Kong as well. This trend is not surprising as Vibrionaceae organisms are widespread in local coastal waters and seafood.[21,22] Seafood—both raw and cooked—features strongly in the local diet, and the local population is known to have a high incidence of chronic liver diseases that are associated with the hepatitis B virus.[23] Thalassaemia disorders are also common.[24] This combination of factors predisposes to infection, and the serious nature of *V vulnificus*-associated necrotising fasciitis makes Vibrionacae infection pose a significant public health hazard in Hong Kong. Preventive advice should be given to people who are in high-risk categories,[25] such as direct warnings to at-risk patients (eg those with liver cirrhosis) by primary physicians, posted warnings in restaurants (in appropriate languages)—even on menus, and the use of the mass media to improve awareness.[25,26] Governmental intervention to enforce and regulate preventive measures may become necessary.[26] In none of the patients described in this series was the correct diagnosis entertained on presentation, thus highlighting the necessity for better education of primary care physicians, emergency department personnel, surgeons, and intensive care specialists with regard to the recognition and management of necrotising fasciitis.

In conclusion, the public, at-risk individuals, and medical personnel should be made aware of the clinical syndrome of necrotising fasciitis caused by marine Vibrionaceae. In Hong Kong, clinical suspicion should always be aroused when a patient presents with a painful and erythematous lesion of an extremity and a history of contact with seafood or an aquatic environment. A history of known risk factors should raise levels of suspicion further. Once the disease is suspected, aggressive investigation, close observation, and treatment with appropriate antibiotics and surgery is essential to ensure survival.

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Final antibiotic/s	Time from admission to surgery	Surgical management	Outcome
Ceftazidime, tetracycline, metronidazole	6 hours	Debridement followed by amputation	Died, day 7
Ceftazidime, netilmicin	12 hours	Debridement followed by amputation	Died, day 15
Ceftazidime, metronidazole	18 hours	Debridement	Died, day 1
Ceftazidime, metronidazole ciprofloxacin	24 hours	Above-knee amputation, mid-thigh amputation, ongoing debridement, hip disarticulation (D12)	Discharged home, day 32
Ceftazidime, metronidazole ciprofloxacin	12 hours	Amputation	Died, day 1
Ceftazidime, metronidazole ciprofloxacin	20 hours	Amputation	Died, day 3

§ Ratio of arterial oxygen partial pressure to fractional inspired oxygen concentration <150
| DIC disseminated intravascular coagulation: platelet count <50x10^6 /L and partial thromboplastin time prolonged for >3 s compared with control value

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