ORIGINAL ARTICLE

Factors affecting mortality in Hong Kong patients with upper limb necrotising fasciitis

CME

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Objective To identify predictive factors for mortality of patients with upper limb necrotising fasciitis.

Design Retrospective study.

Setting Six hospitals in Hong Kong.

Patients Clinical records of 29 patients treated in the hospitals were traced and analysed.

Main outcome measures Possible predictive factors for mortality as evaluated by application of Fisher's test.

Results Overall mortality was 28%. Digital infections conferred a lower mortality, but progressive necrosis necessitated amputation. *Vibrio vulnificus* was the commonest organism identified in association with marine injury and in patients with cirrhosis. Prognostic indicators with decreasing significance include deranged renal and liver function, thrombocytopaenia, proximal involvement (elbow or above) initially, and presence of hypotension upon admission.

Conclusion With a P value of less than 0.05, deranged renal and liver function, thrombocytopaenia, initial proximal involvement, and hypotension on admission were predictors of mortality in necrotising fasciitis affecting the upper limbs. The ALERTS (Abnormal Liver function, Extent of infection, Renal impairment, Thrombocytopenia, and Shock) score with a cutoff of 3 appeared to predict mortality.

Key words
Bacterial infections; Debridement; Fasciitis, necrotizing; Upper extremity; *Vibrio vulnificus*

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Introduction

Necrotising fasciitis is a severe life-threatening infection. Its annual incidence in Hong Kong is 0.53 per 100 000 inhabitants,[1] with a crude death rate of 0.4 per 100 000 in years 2005 and 2006.[2] As a result of anatomical variations, upper limb necrotising infection and infections involving other body parts differ, not only in terms of incidence but also with respect to clinical behaviour and aggressiveness. Our study therefore aimed to evaluate the predictive factors for mortality in relation to necrotising fasciitis involving the upper limbs.

Diagnosis

Necrotising fasciitis is a clinical diagnosis with corroborating operative and histological findings. Fisher et al's five standard diagnostic criteria[3] include: (1) extensive necrosis of fascia with adjacent skin involvement, (2) intoxication with reduced consciousness, (3) absence of muscle involvement, (4) absence of vascular occlusive disease, and (5) histological findings of leukocyte infiltration, focal fascial necrosis and micro-thrombosis. Douglas[4] has emphasised the absence of *Clostridium* in blood and wound cultures, while absence of muscle involvement was not a diagnostic criterion. In contrast, Gillen[5] included *Clostridium* as a causative organism.

A clinical diagnosis can be readily made according to the features listed in the clinical staging proposed by Wong and Wang,[6] based on progressive skin changes due to skin ischaemia. Stage 1 includes cardinal signs of inflammation with erythema, swelling, warmth and tenderness to palpation. Stage 2 is characterised by onset of critical skin ischaemia with blisters or bullae formation. Stage 3 is signified by the onset of tissue necrosis, characterised by 'hard signs' including haemorrhagic bullae, skin anaesthesia or

crepitus, and frankly gangrenous changes.

Intra-operative findings include a lack of fascial bleeding, presence of dishwater pus with greyish necrotic fascia, and minimal resistance to blunt dissection. These findings are also compatible with Andreasen et al's proposal[7] of the 'finger test' for confirmation of the clinical diagnosis of necrotising fasciitis, with a 2-cm incision made down to deep fascia under local anaesthesia, followed by blunt finger dissection.

Histological criteria for diagnosing necrotising fasciitis as described by Stamenkovic and Lew[8] reliably identified even early cases. They include necrosis of the fascia, polymorphonuclear infiltration, fibrinous thrombi of arteries and veins coursing through the fascia, angiitis with fibrinoid necrosis of arterial and venous walls, presence of micro-organisms within the destroyed fascia, and an absence of muscle involvement.

In our study, the diagnoses were made combining both clinical and intra-operative findings, except in one patient with multiple medical problems with a high anaesthetic risk, and in three others with a relatively indolent presentation in whom it was determined histologically. Patients with an incorrect initial diagnosis had a progressive course despite receiving usual antibiotics or surgical drainage, until the diagnosis was revised and an appropriate and radical fasciectomy was performed. Intra-operatively, such patients showed dishwater pus spreading along fascial planes in addition to fascial necrosis. To confirm the diagnosis, in 21 patients specimens were also saved for histology. In all of them, histology revealed fascial and subcutaneous tissue necrosis, together with polymorphonuclear and bacterial infiltration into fascia with microvascular thrombosis.

Methods

On behalf of the Hong Kong Society for Surgery of the Hand working group, we retrospectively retrieved the clinical records of 29 patients treated in six acute Hong Kong public hospitals, who were diagnosed to have necrotising fasciitis of one or both upper limbs. A history of injury to the limb was sought, the site and proximal extent recorded and staged.

The variables that were assessed included: age, gender, premorbid status, smoking and drinking habits, and vital parameters on admission (body temperature and blood pressure). Haematological and biochemical parameters were evaluated with reference to the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score.[9] The types of antibiotics that were used to treat the infection and microbiological culture results of the tissue samples obtained at the time of the first operative debridement were recorded. The number of operative debridements, the decision for amputation and reconstruction, and the in-hospital mortality rate were also documented. In the analysis of prognostic factors for mortality, Fisher's test was used to calculate the P value for each of the variables.

影響上肢壞死性筋膜炎香港患者死亡率的因素

目的 探討上肢壞死性筋膜炎死亡率的預測因子。

設計 回顧研究。

安排 香港其中六間醫院。

患者 在以上醫院應診的29名病人的臨床病歷。

主要結果測量 利用費氏精確檢定評估死亡率的預測因子。

結果 總死亡率為28%。手指感染的死亡率較低，可是漸進性的壞死性筋膜炎最終亦須進行截肢。創傷弧菌（*Vibrio vulnificus*）是與海水有關的創傷性感染及肝硬化病人最經常感染的細菌。預後指標的重要性由大至小依次為腎和肝功能失常、血小板減少症、起初近端牽涉的位置（肘或以上），以及入院時低血壓的情況。

結論 以P值低於0.05為標準，影響上肢壞死性筋膜炎死亡率的預測因子為腎和肝功能失常、血小板減少症、起初近端牽涉的位置，以及入院時低血壓的情況。ALERTS分數（即肝功能失常、感染範圍大小、腎功能損害、血小板減少症、休克）界值為3似乎可以預測死亡。

Results

The present study included 21 men and 8 women. The mean age of the patients was 60 years; 20 had one or more co-morbidities, three were intravenous drug abusers, seven were chronic smokers, and five were ex-smokers.

All except two patients were admitted within 2 hours of initial registration at the Accident and Emergency Department (AED). One patient was misdiagnosed as forearm cellulitis and one as gouty arthritis of the wrist, both of whom were discharged from the AED. Both of these patients re-attended within 2 days with significant disease progression and eventually died. Two other patients were transferred from the medical department, one after an urgent consultation for fever soon after admission, and another who presented with necrotising fasciitis complicating a heparin block insertion.

An initial diagnosis of necrotising fasciitis was correctly made by the first attending orthopaedic surgeon in 15 out of the 29 patients. Other preliminary diagnoses included cellulitis, abscess, tenosynovitis, and gouty arthritis. Twenty-one patients had endured a preceding injury. Eight patients were injured by seafood and two had self-needle injections. On initial

presentation, fever was present in 12 patients and hypothermia in none. Eight patients had hypotension, and 13 had biochemical evidence of organ failure (Table 1).

At the initial presentation, seven patients had infection primarily involving the forearm and two over the arm region; in six of them it was on the dorsal surface. Of the five patients with stage 3 disease on presentation, four died; four patients with stage 1 disease and all survived. Three patients had multiple limb involvement; one had left lower limb and subsequent bilateral upper limb infection, one had concomitant left leg and right arm infection, and one had a preceding buttock infection. Of the 10 patients with hand or wrist dorsum involvement, three had stage 1 disease, two of whom died. Whilst two other patients with stage 2 disease all survived, and out of five with stage 3 disease one died. In all, 10 patients had digits involved initially; in seven the volar surface was affected. Regarding these 10 patients, three, two, and five had stage 1, 2, and 3 disease, respectively, yet all but one survived.

As a predictor of early necrotising infections, the LRINEC score was evaluated for the patients in our study. In most of them it could not be calculated as the C-reactive protein value was not routinely requested on admission. Of the 10 patients who were scored, in five it met the cutoff value of 6, and 14 others had white cell counts of 15 x 10^9/mm^3 or higher. Moreover, 14 patients had haemoglobin levels lower than 135 g/L, 10 had serum creatinine levels higher than 141 μmol/L, and nine (out of 22)

TABLE 1. Initial presentation, systemic manifestations, and laboratory parameters in relation to mortality

Patient No.	Death	Initial site involved*	LFT†	Extent	Creatinine (μmol/L)	Platelet count (x 10^9 /L)	Shock (SBP/DBP) [mm Hg]‡
1	-	L forearm dorsum	-	Below elbow	85	237	-
2	-	R M/F pulp	-	Finger	79	146	-
3	-	R I/F pulp	-	Finger	87	115	-
4	-	R forearm dorsum	Bil 77, ALT 75 (day 1)	Below elbow	106	159	86/50
5	Y	L volar forearm	Bil 85, ALT 121	Below elbow	434	22	Inotropes
6	-	R L/F dorsum	-	Finger	86	236	-
7	-	L elbow dorsum	-	Upper arm	111	138	-
8	-	R buttock, L volar forearm	-	Below elbow	182 (2 x normal)	30	87/45
9	-	R thumb pulp	-	Thumb	76	154	-
10	-	L wrist dorsum	Bil 88 (day 4)	Axilla	172 (1.4 x normal)	196	-
11	-	L hand 1st web space	-	Forearm	123	256	-
12	Y	L leg, bilateral volar forearm	ALT 94 (day 12)	Arm	307	106	62/41
13	Y	L hand dorsum	ALT 351	Chest wall	146 (1.5 x normal)	32	-
14	-	R I/F pulp	-	Finger	64	267	-
15	-	R hand dorsum	-	Half forearm	77	227	-
16	Y	R hand dorsum	Bil 138, ALT 96 (day 2)	Elbow	208	85	67/38
17	Y	L forearm dorsum	-	Axilla	168 (1.5 x normal)	111	MAP 67
18	-	R I/F pulp	-	Finger	61	406	-
19	Y	L thumb pulp	Bil 52, ALT 137	Elbow	99	61	-
20	-	R hand dorsum	-	1/3 Forearm	108	337	-
21	-	R forearm dorsum	-	Elbow	78	308	-
22	Y	R wrist dorsum	Bil 25, ALT 60 (day 3)	Elbow	221	50	Inotropes
23	-	R wrist dorsum	-	Forearm	123	59	-
24	-	R I/F dorsum	-	Forearm	82	270	-
25	Y	L leg, R elbow	Bil 31, ALT 146	Arm	214	87	Inotropes
26	-	L R/F dorsum	-	Finger	43	204	-
27	-	L hand dorsum	-	Deltoid	205	204	-
28	-	R thumb pulp	-	Finger	109	67	-
29	-	L hand dorsum	Bil 23, ALT 78 (day 2)	Forearm	105	169	-

* M/F denotes middle finger, I/F index finger, L/F little finger, and R/F ring finger

† LFT denotes liver function test, Bil bilirubin (in μmol/L), and ALT alanine aminotransferase (in U/L)

‡ DBP denotes diastolic blood pressure, SBP systolic blood pressure, and MAP mean arterial pressure

had serum glucose levels higher than 10 mmol/L.

Positive local specimen cultures were obtained in all but one patient (Table 2). *Candida* was identified in one patient with a history of systemic lupus erythematosus complicated by nosocomial pneumonia, who eventually died. Regarding the remaining 27 patients, four samples entailed type I polymicrobial infections (group B *Streptococcus* from 2, and *Streptococcus milleri*). There were eight samples that grew type II infection microbes (group A *Streptococcus* alone in 4 and 4 that were co-infected with *Staphylococcus aureus*). There were nine infections caused by marine micro-organisms, eight entailed *Vibrio vulnificus* and one *Aeromonas hydrophila*. The remainder entailed isolated growths (*S aureus*, *Pseudomonas aeruginosa*, *Edwardsiella*, and *Acinetobacter baumannii*). Blood culture was performed in 22 of these patients but less than half yielded a positive growth.

For the sensitivity pattern, fluorinated quinolones demonstrated the widest spectrum of activity; 16 out of 18 organisms tested (vibrios, streptococci, staphylococci, *P aeruginosa*) were sensitive, but not *A baumannii*. Amoxycillin/clavulanate (Augmentin; GSK, Worthing, West Sussex, UK) was also considered useful, as six out of eight organisms tested were sensitive, including vibrios, streptococci, staphylococci and *Edwardsiella*, but not *A hydrophila* and *A baumannii*. No group A streptococci were resistant to penicillin.

TABLE 2. Microbiology, sensitivity to antibiotics, and co-morbidities in relation to mortality

Patient No.	Death	Co-morbidities*	Injury	Organism†	Augmentin/ Unasyn	Cipro-/levo-floxacin	Penicillin
1	-	-	Knife	Ah	N	Y	-
2	-	-	Fish fin	Vv	-	Y	-
3	-	HBV cirrhosis	Fish fin	Vv	Y	Y	-
4	-	HBV cirrhosis	-	Vv	-	Y	-
5	Y	-	Injection	GAS	-	Y	Y
6	-	HT, gout, CVA	Abrasion	Sa/GAS	-	Y / Y	N / Y
7	-	-	-	Sa	-	Y	N
8	-	-	Injection	Ab	N	N	-
9	-	HT, DM, IHD	Fish fin	Pa	-	Y	-
10	-	IHD, hyperlipidaemia	-	GAS	Y	Y	Y
11	-	-	Pork hook	Sa/GAS	-	-	N / Y
12	Y	HT, AF, asthma	-	*Edwardsiella*	Y	Y	-
13	Y	HT, DM, IHD	Hep block	GAS	-	-	Y
14	-	HT, ureteric stone	Fish sting	Vv	-	Y	-
15	-	HT, DM	Fish teeth	Vv	-	Y	-
16	Y	HT, IHD, CHF	Crab sting	Vv	-	Y	-
17	Y	HT, DM, ACS, CHF	Contusion	GAS	-	-	Y
18	-	HT, DM, IHD	Rubbish	Sm/En	-	-	Y / -
19	Y	Cirrhosis, splenectomy	Fish	Vv	Y	Y	-
20	-	-	-	Sa/GBS	-	-	- / Y
21	-	HT, DM, angina	Injection	Sa	-	-	-
22	Y	SLE, nephritis	Hep block	*Candida*	-	-	-
23	-	HT, DM, IHD, cirrhosis	Hep block	Sa	-	-	-
24	-	-	-	GAS/Sa/GGS	-	-	-
25	Y	DM	-	Cocci	-	-	-
26	-	DM	Hot oil	Sa/GBS	- / Y	N / Y	-
27	-	Addison's disease	Contusion	Sm/Haem/Vei	- / Y / -	-	Y / Y / -
28	-	DM	Fish	Vv	-	Y	-
29	-	-	-	Sa / GAS		-	Y / -

* HBV denotes hepatitis B virus, HT hypertension, CVA cardiovascular accident, DM diabetes mellitus, IHD ischaemic heart disease, AF atrial fibrillation, CHF congestive heart failure, ACS acute coronary syndrome, and SLE systemic lupus erythematosus

† Ah denotes *Aeromonas hydrophila*, Vv *Vibrio vulnificus*, GAS/GBS/GGS group A/B/G *Streptococcus*, Sa *Staphylococcus aureus*, Ab *Acinetobacter baumannii*, Pa *Pseudomonas aeruginosa*, Sm *Streptococcus milleri*, En *Enterobacter*, Haem haemophilus, and Vei *Veillonella*

The total number of debridements performed per patient (including the initial operation) ranged from 1 to 7, with a mean value of 2. In all, 11 amputations were performed; three were above-elbow, two were below-elbow, and six entailed digits. Reasons for amputation included the presence of non-viable underlying necrotic muscles, extensive rapidly progressive skin necrosis with gangrenous changes, and if inotropic support was deemed necessary. Thrombosis of bilateral digital arteries was observed in five of the amputated digits. In one patient the necrotic ring finger was sacrificed for fillet flap reconstruction. Fourteen patients had wound resurfacing after serial debridement; in 10 this entailed a skin graft and four it was by flap coverage.

Fourteen out of these 29 patients received intensive care unit (ICU) support, which included eight out of 11 individuals with necrotising fasciitis extending proximal to the elbow; seven of the latter eight died. Ten patients had necrotising fasciitis of the forearm, but not extending proximally to the elbow region; five received ICU support, only one of whom died. Of the remaining patients, only one was admitted to the ICU and survived. Of the 21 survivors, 14 were discharged within 1 month of admission.

Discussion

In our series, the overall mortality for upper limb necrotising fasciitis was 28%. This, however, also included 10 patients with digital infections who had relatively low mortality. Excluding the latter increased the rate to 37%, which still compares favourably with other reports from Asia (36 and 33% in reference to mixed upper and lower limb involvement, respectively).[1,10,11]

TABLE 3. Prognostic indicators in relation to mortality

Prognostic factor	P value (Fisher's test)	Relative risk	Odds ratio
Mean age >60 years	0.7	1.354	1.515
Positive smoking history	1.0	1.000	1.000
Diabetes	1.0	1.140	1.200
Cardiovascular disease	0.67	1.333	1.500
Shock	0.001	7.875	28.50
Fever ≥38°C	0.22	2.361	3.333
Involvement of elbow or above	0.001	11.45	29.75
Stage 3 on presentation	0.21	2.800	4.000
Skin necrosis	0.68	1.417	1.625
Vibrios infection	1.00	1.000	1.000
Positive blood culture	0.14	4.800	7.333
Platelet count <150 x 10^9 /L	0.001	-	-
Creatinine ≥1.5 x normal	<0.001	15.56	66.50
White blood cell count ≥15 /mm^3	1.00	0.750	0.682
Sodium <135 mmol/L	1.00	0.844	0.800
Deranged liver function test	<0.001	13.30	42.00
International normalised ratio ≥1.6	0.30	2.100	3.750
Antibiotics following guidelines	0.30	2.300	3.600
Amputation (excluding digits)	1.00	1.120	1.200

Clinical presentation

Our study concluded that mortality was significantly related to extent of tissue involvement; a poor prognosis was evident (P=0.0014) whenever the infection extended to the elbow or above just before the time of operation (Table 3), which was similar to Tang et al's findings.[1] Like the initial anatomical site involved, the rapidity of the infective process is also highly predictive of mortality. We observed that infections initially involving the forearm or wrist were associated with increased mortality compared to infections at the digital level, while there was no statistically significant difference between infections at the hand or wrist level compared to the forearm. Necrotising fasciitis of the hand and dorsum of the wrist behaved like forearm infections in that they were rapidly progressive, and tracked up the fascial plane of the wrist, which lies in a continuum with the dorsum of the forearm. In contrast, we did not find clinical staging (including the presence of skin necrosis) correlating with mortality.

Upper limb necrotising infections commonly follow local trauma. Their anatomy as well as their functional roles make upper limbs susceptible to injury. In our series, 21 patients reported a previous injury; 17 endured penetrating trauma and four had blunt injuries. The proportion of remaining cases with spontaneous infections in uninjured intact skin was higher than the 11% reported in a systematic review of necrotising fasciitis of the extremities.[12] Regarding specimens from our eight patients with fish- or crab-associated injury, all but one grew vibrios. In addition, in seven out of these 10 patients, the digital injury was on the volar aspect, while more proximal injuries usually involved the dorsal side. This may be explained by the different anatomical locations resulting in varying chances of exposure to potential hazards, whilst injuries to the finger dorsum and the volar side of forearm are relatively rare during usual daily activities.

The clinical diagnosis of necrotising fasciitis remains difficult. In our series an initial diagnosis of necrotising fasciitis in the upper limbs was correctly made in only half of the patients. One reason is that the spectrum of infections exists along a continuum of clinical severity with different aetiological agents and associated medical conditions. Early necrotising infections may mimic a spectrum of other infections from cellulitis to abscess. Infection is confined to

the fascial layer below the overlying skin on early presentation, and inspection may reveal subtle findings. Diagnosis of necrotising fasciitis of the digits and hands can be particularly challenging, as a wide range of differential diagnoses may be under consideration in view of the multiple anatomical structures in a relatively confined space.

Systemic manifestations may provide a clue, but in upper limb necrotising infections they are not particularly common. In our study, fever was present in 41% of the patients, compared to 35% and 53% in two other series.[6,13] Although Wong and Wang[6] mentioned that previous literature stressed systemic manifestations as important clues, doctors should appreciate that patients can appear systemically quite well. Broad-spectrum antibiotics prescribed at the primary care level may reduce the bacterial load and the liability to organ failure, although the primary site of pathology remains untreated and liquefactive necrosis blocks tissue penetration of antimicrobials. The initial presentation also depends on the time interval between injury and hospital admission, as well as the patient's immunological status. Thus, patients in the early course of the disease may present with only mild symptoms and no systemic toxicity.[14] Without receiving appropriate initial treatment, the disease progresses and bacteria spread. Upon hospital admission the extent of fascial invasion by bacteria reflects the severity of bacterial loading, whilst the production of more and more toxins causes organ impairment and systemic manifestations.

In our series, erythema and tenderness were early and consistent features. Pain may be out of proportion to other clinical findings, as the pathology usually involves the fascia before any apparent overlying skin changes. Tenderness can be present and extend beyond the apparent area of infection, as the bacteria rapidly proliferate within the fascia with initial sparing of the skin. Interval assessment helps by showing rapid spread of the infection despite usual antibiotics regimens. The development of blisters or bullae is an important diagnostic clue. In our series, 16 of the 30 involved upper limbs developed blisters. Blisters are caused by ischaemia-induced necrolysis due to progressive perforator vessel thrombosis by invading organisms. This is rarely encountered in cellulitis or erysipelas. The late stage is characterised by 'hard signs' including haemorrhagic bullae, skin anaesthesia or crepitus and, frank gangrenous changes. Postulated diagnostic adjuncts include the 'finger test'[7] and frozen section biopsy.[8] In our Hong Kong series, these were not commonly pursued, possibly due to associated morbidities, lack of immediate support from pathologists, and a high rate of negative biopsies. The use of the LRINEC score (mentioned below) may also be a diagnostic adjunct, although such a role is still not well-established in upper limb necrotising infections.

Laboratory findings

Besides the primary pathology, systemic manifestations including hypotension and organ failure were also associated with increased mortality (Table 3). According to the International Sepsis Definitions Conference (ISDC) in 2001,[15] arterial hypotension in sepsis is defined by a systolic blood pressure of less than 90 mm Hg or mean arterial pressure of less than 70 mm Hg, and correlates with increased mortality (P=0.0014). Thrombocytopaenia was also shown to correlate with increased mortality (P=0.0007). The relationship between thrombocytopaenia and sepsis has been defined, and is associated with a mortality rate as high as 38 to 54%, depending on the degree of thrombocytopaenia.[16,17] In contrast, the definition of deranged renal and liver function appears to be more complex, owing to a lack of international agreement. The ISDC recommends serum creatinine levels increasing by more than 44.2 μmol/L as the diagnostic criterion for sepsis. We adopted a newer and more sophisticated definition for deranged renal function, based on the RIFLE (risk, injury, failure, loss, ESRD) criteria by the Acute Dialysis Quality Initiative group in 2004.[18] 'R' stands for 'risk of renal dysfunction', and is defined by an elevated serum creatinine level of 1.5 times or higher than the upper limit of normal range adjusted for the patient's age, gender, and body build. With a P value of 0.0002, deranged renal function was statistically associated with mortality. Deranged liver function was also related to mortality (P=0.0005). It was defined as hyperbilirubinaemia with a total serum bilirubin of more than 70 mmol/L (the ISDC definition), or an elevation of hepatic enzymes exceeding the upper limit of normal 2-fold. In a univariate analysis of 150 patients with necrotising fasciitis of the extremities, hypotension, low bicarbonate level, as well as elevated blood urea nitrogen, creatinine, aspartate aminotransferase and potassium levels were associated with increased mortality.[19] These results were also compatible with our findings.

The ALERTS (Abnormal Liver function, Extent of infection, Renal impairment, Thrombocytopenia, and Shock) numerical score was proposed for use in our study as a means of predicting associated mortality, with each parameter bearing a score of one and summed score of up to five (Table 4). In our study, all patients with mortality had an ALERTS score of 3 or more. Among the survivors, one patient had a score of 3, four had a score of 2 and six had a score of 1. The positive predictive value was 89% (8/9) and the negative predictive value was 100% (20/20). With a cutoff value of 3, the ALERTS score alerts physicians to increased mortality (P=0.0001; Fisher's test). An advantage of this scoring system is that all

parameters can be measured preoperatively and it is effective in predicting mortality, except that liver function abnormalities may take a few days to rise. In our study though, most patients who succumbed had deranged liver function tests within 3 days of their initial operation.

Fisher's exact test was applied in our study, which overcomes the drawback of small sample sizes, while still enabling detection of statistical significance. It has therefore been adopted to assess factors associated with mortality,[1,6,19] with sample sizes as small as 24.

Premorbid factors

In contrast to another report from Hong Kong,[1] our series reported no correlation between mortality and co-morbidities or advanced age. Wong et al's study[20] also suggested that advanced age, and two or more associated co-morbidities affected outcome adversely. Diabetes was the most common co-morbidity (affecting 10 of our patients), whereas four had liver cirrhosis (3 of whom developed *Vibrio* infections). Other co-morbidities included chronic cardiac disease, chronic steroid therapy, systemic lupus erythematosus, and Addison's disease.

Microbiological pattern

Type I infections are polymicrobial, synergistic infections that are usually caused by non–group A streptococci, aerobic organisms, and anaerobic organisms. Type II infections are caused by *Streptococcus pyogenes* alone or with staphylococci.[20] A further type of infection, caused by marine vibrios, is usually associated with seawater or marine animal exposure. Although our study failed to establish a relationship between mortality and any specific microbiological species, we believe that marine vibrios (particularly *V vulnificus*) give rise to a more fulminating course than group A *Streptococcus* infections.[21] A confining factor was the anatomical site involved, since marine organism injuries usually occurred over the digits, and as previously mentioned the latter were associated with a relatively low mortality. Notably, infections caused by group A *Streptococcus* nevertheless give rise to high morbidity and mortality.[22]

Our study also evaluated the efficacy of different treatment methods, including antibiotics and surgery as predictors of mortality. The Infectious Diseases Society of America Guidelines[23] has been adopted in western countries, and states that the best choice for a community-acquired mixed infection was a combination of ampicillin-sulbactam (Unasyn; Pfizer, Borgo San Michele, Italy) plus ciprofloxacin plus clindamycin (level A-III evidence). For monomicrobial necrotising fasciitis caused by group A streptococci, both clindamycin and penicillin should be used (level A-II evidence). With a prior history of exposure to seawater or intra-abdominal operations, the IMPACT (Inter-hospital Multi-disciplinary Programme on Antimicrobial ChemoTherapy) Guidelines published in Hong Kong advocate the use of intravenous amoxicillin-clavulanate and a fluoroquinolone for treating necrotising fasciitis patients. The latter antimicrobials provide cover against Gram-negative bacilli (including vibrios). Whereas, in healthy patients with recent cuts or abrasions and for intravenous addicts, intravenous penicillin G and clindamycin should be used to cover Gram-positive organisms (most commonly group A *Streptococcus*). The Gram stain result of pus or deep wound tissue (obtained during surgery) can also guide the initial antibiotic therapy.[24]

Regarding the use of antibiotics and mortality in suggested guidelines, the P value was 0.30, which was not statistically significant. We nevertheless observed that antibiotic regimens used in a number of our patients were inconsistent, frequently adjusted, and entailed inadequate dosages and treatment durations. In addition, use of different classes of antibiotics further confused the picture. Our study therefore focused on the sensitivity pattern of the organisms with respect to recommended antibiotics. In our series of patients, six out of eight isolates tested for sensitivity to Augmentin (GSK) were susceptible, and similarly 16 out of 18 tested organisms were sensitive to quinolones; all eight *Vibrio* species isolated were sensitive to either ciprofloxacin or levofloxacin.

TABLE 4. The ALERTS (Abnormal Liver function, Extent of infection, Renal impairment, Thrombocytopenia, and Shock) score*

Variable†	Score
Abnormal liver function	
Bilirubin <70 mmol/L and normal ALT/AST	0
Bilirubin ≥70 mmol/L or ALT/AST >2 x normal	1
Extent of infection	
Below elbow	0
Elbow or above	1
Renal impairment	
Serum creatinine <1.5 x normal	0
Serum creatinine ≥1.5 x normal	1
Thrombocytopaenia	
Platelet count ≥150 x 10^9 /L	0
Platelet count <150 x 10^9 /L	1
Shock	
SBP ≥90 mm Hg or MAP ≥70 mm Hg	0
SBP <90 mm Hg or MAP <70 mm Hg or inotropes support	1

* A cutoff score of ≥3 was predictive of increased mortality (note: deranged liver function may take a few days to manifest)

† ALT/AST denotes ratio of alanine aminotransferase/aspartate aminotransferase, SBP systolic blood pressure, and MAP mean arterial pressure

Group A *Streptococcus* was identified from six patients and all were sensitive to penicillin, although two of the patients were also co-infected with penicillin-resistant *S aureus*. Susceptability to clindamycin could not be evaluated since most laboratories in Hong Kong did not perform sensitivity testing for this drug. We therefore recommend quinolones and Augmentin (GSK) as the empirical treatment for necrotising fasciitis, and penicillin for monomicrobial or polymicrobial group A *Streptococcus* infections. Readjustment of the antibiotic regimen can always be performed when culture and sensitivity patterns become available.

Treatment outcomes

The timing of surgical debridement appears important for survival. In our study, there was no clear-cut time delay in relation to mortality. However, we believe that delaying to operate allows the infection to extend proximally resulting in decreased chance of survival. This observation is also supported by other studies,[20,25] which showed that a 24-hour delay in surgery correlated with increased mortality.

Although necrotising fasciitis of the digits had a low mortality, it can present with progressive gangrenous changes, despite the use of intravenous antibiotics and early debridement. Thrombosis of both digital arteries was observed in five amputated digits, which we believe might be an under-reported phenomenon. Macrovascular thrombosis of digital arteries and microvascular necrosis of skin perforators appear to be the underlying pathology of progressive cutaneous necrosis, which eventually becomes an indication for amputation. In our study, other than for digits, amputation was not found to reduce mortality; the P value was 1.0 when digital amputations were excluded. The criteria for amputation recommended by Tang et al[1] were adopted. These included: concurrent medical disease with high anaesthetic risk, extensive soft tissue necrosis with involvement of the underlying muscles, shock deemed to require treatment with more than one inotrope, concurrent vascular insufficiency, and a rapidly progressing infection with a large area of tissue necrosis. In our series, there were three above-elbow and two below-elbow major amputations, in addition to six digital amputations. Amputation was usually considered a shorter procedure associated with less blood loss than a radical debridement. Patients in profound shock-receiving inotropes and those with severe concurrent medical diseases may not tolerate protracted operations. Despite aggressive surgical intervention, two out of four patients in our series who underwent major amputation died. While amputation was not found to reduce mortality, patients who underwent this procedure had fewer operations to control the infection and achieve wound coverage.[20]

Conclusion

Our study suggested that mortality is related to deranged renal and liver function, thrombocytopaenia, initial proximal involvement extending to the elbow or above, and the presence of hypotension on admission. We believe that the underlying cause was related to extensive infection with systemic disturbance, which was reflected by biochemical derangement, multi-organ failure and hypotension despite aggressive fluid resuscitation. The width of involvement predicts mortality, while the depth guides amputation. The ALERTS score with a cutoff of 3 was proposed as a predictor of mortality.

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