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CASE REPORT

Tigecycline salvage therapy for necrotizing fasciitis caused by *Vibrio vulnificus*: Case report in a child

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Necrotizing fasciitis caused by *Vibrio vulnificus* is rarely reported in children. We describe a 12-year-old immunocompetent boy with necrotizing fasciitis caused by *V. vulnificus*. He was cured by radical and serial debridement and salvage therapy with intravenous cefpirome plus tigecycline. The *in vitro* antibacterial activity of combination regimens and a literature review of pediatric *V. vulnificus* infection are described.

Introduction

Vibrio vulnificus is a halophilic, bacillary, Gram-negative bacterium that is endemic and increasingly prevalent in warm estuarine and marine environments throughout the world. The bacterium has a commensal relationship with marine and estuarine sea life along the coast of Taiwan. Necrotizing fasciitis caused by *V. vulnificus* is rarely reported in children. Traditional therapy with a third-generation cephalosporin combined with minocycline is usually synergistic and effective. We report the case of a 12-year-old boy with rapidly progressive necrotizing fasciitis caused by *V. vulnificus* who exhibited a poor response to ceftazidime plus minocycline. However, salvage therapy with cefpirome plus tigecycline can stabilize wound conditions. *In vitro* antimicrobial susceptibility and a time-killing study of combination therapy were assessed and

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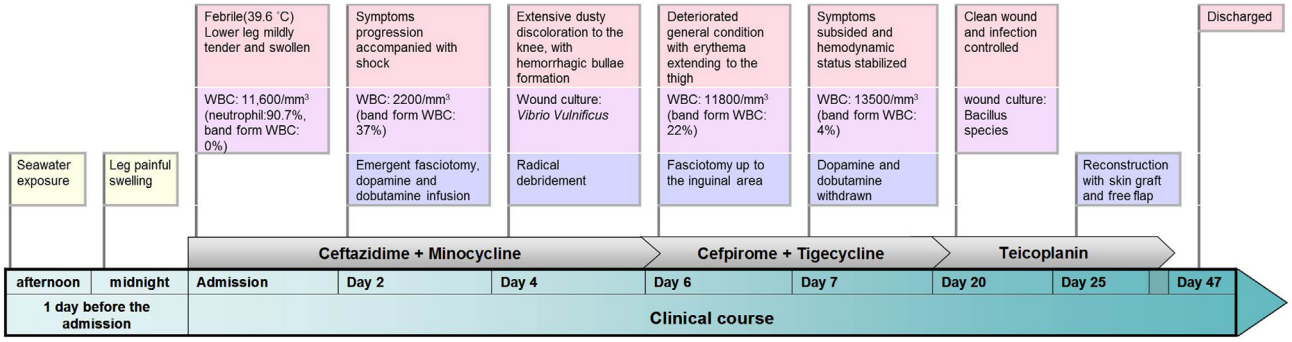

Figure 1. Summary of the clinical course in our patient.

carried out a literature review of pediatric *V. vulnificus* infection.

Case report

A 12-year-old boy without underlying disease was injured by wooden stick penetration of his left leg. The same afternoon, he handled shrimps at the fish market. Painful swelling of his left leg developed by midnight, and he was sent to the emergency department for evaluation.

On physical examination, he looked ill and was febrile, with a body temperature of 39.6°C, pulse rate of 79 beats/min, respiratory rate of 22 breaths/min, and blood pressure of 110/58 mmHg. His left lower leg was mildly tender and swollen with no obvious open wounds. Initial laboratory studies showed a hemoglobin level of 11.6 g/dL, hematocrit of 44.5%, white blood cell (WBC) count of 11,600/mm^3 (neutrophils 90.7%, band form WBCs 0%, and lymphocytes 5.5%), platelet count of 262,000/mm^3, and serum C-reactive protein of 0.9 mg/dL (normal range $<$ 6 mg/dL). Blood culture results were negative. An emergency consultation with a plastic surgeon was arranged because of progression of swelling and pain. The leg was very tender and a dusky discoloration was noted on the upper lateral part of the leg. In addition, the patient was in shock. An emergency fasciotomy was performed and intravenous ceftazidime (1 g every 8 hours) with minocycline (80 mg every 12 hours) was immediately administered. On Day 4 following admission, the dusty discoloration extended to the left knee, with hemorrhagic bullae developing circumferentially in the left leg and dorsal foot. We performed radical debridement of all the necrotic skin and subcutaneous tissue because of the uncontrolled infection. A wound culture revealed *V. vulnificus*. The patient's condition deteriorated further, with erythema extending to the left thigh and inguinal area on Day 6. Therefore, we escalated the antibiotic therapy to cefpirome (2 g every 12 hours) and tigecycline (40 mg every 12 hours) and performed another fasciotomy in the erythematous areas in the inguinal region.

The infection gradually abated. Because of the partial loss of gastrocnemius muscle with exposure of the Achilles tendon, we performed a mesh split-thickness skin graft (with 1:3 expansions) following right latissimus dorsal free flap coverage of the Achilles tendon. The patient was discharged uneventfully on Day 47 and was monitored in the outpatient clinic. Fig. 1 summarizes the clinical course of this disease.

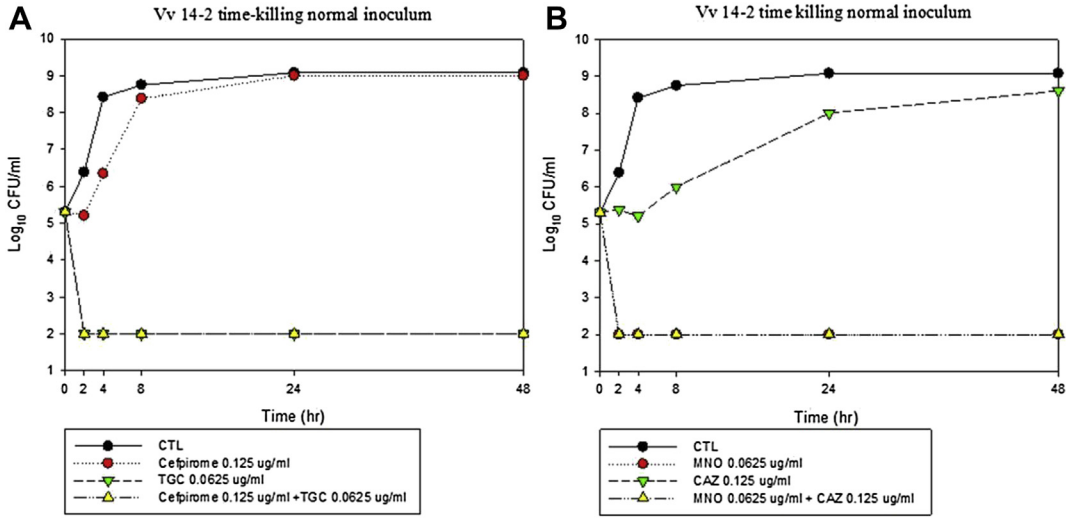

Figure 2. Time-killing curves for 2 $\times$ 10^5 CFU/ml *Vibrio vulnificus* (Vv 14-2) co-cultivated with (A) 1/2 MIC of cefpirome or/and tigecycline alone for 48 hours and (B) 1/2 MIC of ceftazidime and/or minocycline for 48 hours.

Discussion

In vitro susceptibility studies

Initially, we suspected high minimal inhibitory concentrations (MICs) of ceftazidime and minocycline for the isolate. However, we checked the MICs for ceftazidime, minocycline, cefpirome, and tigecycline by the agar dilution method and found low MIC values for all four antimicrobial agents (minocycline 0.125 μg/mL, tigecycline 0.125 μg/mL, cefpirome 0.25 μg/mL, and ceftazidime 0.25 μg/mL). Moreover, MICs measured by the macrodilution method with a high inoculum of 1×10^7 CFU/mL, simulating severe infection with a high bacterial load, were similar for minocycline (0.5 μg/mL) and tigecycline (0.5 μg/mL). However, the MICs for ceftazidime and cefpirome at a high inoculum were 16- and 32-fold higher, respectively, than for a standard inoculum.

Time-killing studies were used to evaluate the antibacterial effect of two combination regimens (Fig. 2). At the concentration of 1/2 MIC for each drug, compared to bacterial regrowth in the presence of cefpirome or ceftazidime alone, tigecycline (Fig. 2A) or minocycline alone (Fig. 2B) exerted rapid antibacterial activity against this *V. vulnificus* isolate. For combination regimens, we can only conclude that no antagonism occurred. Two factors may explain the *in vitro* and *in vivo* treatment discrepancy. First, the concentration we used in the time-killing study was 1/2 MIC, which is lower than serum levels achieved in humans. Therefore, the *in vivo* effect seems to be better. Second, tigecycline has an immunomodulation effect that may explain the discrepancy.

Literature review

To date, only six children with necrotizing soft tissue infections caused by *V. vulnificus* have been described (Table 1).[1–5] Three children had an underlying illness, including nephritic syndrome, thalassemia major, and congenital spherocytosis,[1,2] but three cases, including our patient, had no underlying disease. Intriguingly, four children progressed rapidly to septic shock, but only one expired; another patient underwent an above-the-knee amputation. Except for one patient, all the others had exposure histories consisting of consumption of undercooked seafood, seawater contact, or direct invasion through a wound.

Traditionally, combination therapy with a third-generation cephalosporin and tetracycline or its analogs has an *in vitro* synergistic effect against *V. vulnificus* and is more effective than single-agent therapy for serious infections.[6] With regard to the poor response to standard minocycline and ceftazidime therapy in our patient, we suppose that high soft-tissue concentrations and the cytokine immunomodulation effect of tigecycline could be important factors. However, further animal studies should be performed to confirm this hypothesis. Tigecycline, a member of a new antibiotic class of glycylcyclines, exhibits good tissue penetration and potent antibacterial activity against *V. vulnificus*.[7] For skin and soft-tissue infections, high tissue concentrations of tigecycline have been documented.[8] However, clinical application of tigecycline for

Table 1 Characteristics of soft tissue infections caused by *Vibrio vulnificus* in children

Patient	Age (y)	Sex	Exposure	Underlying disease	Initial symptoms	Septic shock	Antibiotics	Outcome	Ref.
1	12	Male	Consumption of undercooked shrimp	None	Spiking fever, tenderness, swelling	Within 48–h	Ceftazidime plus doxycycline	Survival, skin grafting	3
2	8	Male	Dirty wound	None	Fever, chills, swelling, tenderness, blisters	Within 48–h	NA	Survival, skin grafting	4
3	6.5	NA	NA	Thalassemia	Fever, hematoma	NA	NA	Survival	1
4	17	Male	Working in a fish pond	Congenital spherocytosis	Fever, painful swelling	Within 48–h	Amoxicillin/clavulanate	Survival, AK amputation	2
5	9	Female	Barefoot on a beach	Nephrotic syndrome	Fever, chills, edematous changes, hemorrhagic bullae	None	Ceftazidime plus minocycline	Expired	5
6	12	Male	Shrimp selling after blunt trauma	None	Fever, tenderness, swelling	Within 48–h	Cefpirome plus tigecycline	Survival, LD free flap, skin grafting	Present report

NA = data not available.

invasive *Vibrio* infections has not been reported before. The clinical progression of necrotizing fasciitis in the present case was halted by the combination regimen of cefpirome plus tigecycline. An *in vitro* time-killing study demonstrated rapid antibacterial activity of tigecycline against the causative isolate and no antagonism for the combination of tigecycline and cefpirome.

It is well known that an excess of pro-inflammatory cytokines induced by Gram-negative bacteria is associated with the clinical manifestations of septic shock and increased mortality.[9] Tetracycline and its derivatives, such as minocycline, a bacteriostatic antibiotic, have not only antibacterial but also immunomodulatory effects.[10] In a murine *in vivo* model of *V. vulnificus* infection, peritoneal fluid cytokine levels in the cefotaxime—minocycline combination therapy group were significantly lower than in groups treated with cefotaxime or minocycline alone.[11] In addition, tigecycline altered cytokine production and reduced T-cell proliferation *in vitro*, suggesting an immunomodulatory effect independent of its antimicrobial effect.[12] Such immunomodulatory activity of tigecycline could have contributed to the excellent therapeutic response of our patient. Thus, tigecycline-based therapy, alone or in combination, may be one option for treatment of invasive *V. vulnificus* infections.

In conclusion, necrotizing soft tissue infections caused by *V. vulnificus* are extremely rare in children, and immunocompetent children may be affected. In addition to the combination of a third-generation cephalosporin and tetracycline or its analogs, tigecycline-based salvage therapy may be considered as an alternative choice for invasive infections.

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