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Group A streptococcal necrotizing fasciitis complicating primary varicella: a series of fourteen patients

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We retrospectively reviewed the clinical course of group A *Streptococcus* necrotizing fasciitis complicating primary varicella in children admitted to Children's Hospital and Medical Center, Seattle, WA, during a 18-month period. The potential benefit of various therapeutic interventions was examined. Fourteen children ages 6 months to 10 years were treated for group A *Streptococcus* necrotizing fasciitis as a complication of primary varicella. Eight patients experienced a delay in initial diagnosis as a result of nonspecific, early clinical findings of necrotizing fasciitis. Each patient underwent surgical exploration with fasciotomies and debridement. Initial antibiotic therapy was broad spectrum and included clindamycin. Hyperbaric oxygen therapy for as many as 6 treatments was used as adjunctively therapy in 12 patients, with subjective benefit in 6 patients. All 14 patients were discharged home with good function and no long term sequelae. This potentially fatal bacterial infection of the deep fascial layers requires early recognition by primary care physicians and an intensive, multidisciplinary therapeutic approach, including thorough surgical debridement and appropriate antibiotic therapy.

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INTRODUCTION

Necrotizing fasciitis caused by group A streptococcus (GAS) is a rapidly progressive, potentially fatal infection that may be increasing in frequency.[1–3] In Los Angeles County during 1994, five children died of this infection.[4] Necrotizing fasciitis is characterized by mi-

crobial and leukocytic infiltrates of the superficial fascial and deep dermal layers of the skin with resultant thrombosis, vasculitis and necrosis.[5, 6] The high morbidity and significant mortality of necrotizing fasciitis and other invasive GAS infections are to a large extent toxin-mediated.[7]

Successful management of necrotizing fasciitis hinges on early clinical detection and rapid application of established therapies, but delays in diagnosis are common.[6, 8] Definitive diagnosis is made most rapidly by means of surgical exploration.[6, 8] Treatment consists of thorough surgical debridement, appropriate parenteral antibiotics and intensive supportive care. Additionally hyperbaric oxygen (HBO) therapy has been used in some patients as an adjunct to the standard treatment of necrotizing fasciitis, although its effectiveness has not been established.[6, 9–11]

We summarize the clinical course and medical management of 14 children treated at Children's Hospital and Medical Center in Seattle after developing GAS necrotizing fasciitis as a complication of primary varicella. The potential therapeutic benefits of various interventions in GAS necrotizing fasciitis is discussed from a clinical and biologic perspective.

METHODS

The charts of all patients admitted to our institution with the diagnoses of GAS necrotizing fasciitis and varicella from December, 1993, until May, 1995, were reviewed for demographic information, duration of varicella, presenting secondary symptoms, location of fasciitis and outpatient therapies. Inpatient course was reviewed, including leukocyte count, culture results, surgical procedures, intensive care unit course, antibiotic therapy, HBO treatments and clinical outcome. Two representative case histories are presented.

CASE HISTORIES

Patient 1. A 6-year-old girl with varicella presented to an outside emergency department on Day 6 of skin lesions with spreading erythema of the lateral right thigh. She was discharged home to receive oral cephalexin, acyclovir, acetaminophen and ibuprofen. She returned the following afternoon with worsening erythema, severe pain of the right thigh and inability to walk. Her right thigh had a *peau d'orange* appearance with erythema extending across the lower abdomen to the left thigh. A roentgenogram of the right thigh showed loss of soft tissue planes.

The patient received parenteral antibiotics at an outside hospital and was transported to Children's Hospital on the following morning at which time she required endotracheal intubation because of clinical deterioration. Antibiotic coverage was broadened to clindamycin, gentamicin and ampicillin. She was taken to the operating room where the area of induration on her right thigh was incised down to and including the muscular fascia. The underlying muscle was viable. All areas of necrotic superficial fascia and subcutaneous tissue with the overlying devitalized skin were debrided in an area of approximately 10 by 20 cm.

After surgery the patient developed hypotension, which responded to fluid and dopamine infusions. Because of the severity of clinical symptoms and the association of abdominal wall necrotizing fasciitis with anaerobic organisms, HBO therapy of 2.4 atmospheres at 12-hour intervals for four treatments was instituted. The erythema of the right thigh and abdomen receded in a stepwise fashion by approximately 2 to 3 cm in temporal association with each HBO treatment. After 48 hours inotropic support was discontinued, and the following day she was extubated. Wound cultures grew GAS but blood cultures were negative.

The remainder of the patient's hospital course was uncomplicated. Her wounds were covered with split thickness skin grafts on Postoperative Day 13, and she was discharged home 10 days later with no loss of function and excellent graft viability.

Patient 2. This previously healthy 8-year-old boy developed a fever to 40°C and pain in his right foot on the fourth day of his varicella exanthem. His pediatrician found minimal tenderness and swelling of his right foot and calf with no erythema. A roentgenogram of the foot was normal and he was discharged home to be treated with ibuprofen.

That same evening he was seen in the emergency department for increased pain, erythema and tense edema of the foot and leg to the knee. Compartment pressures were found to be elevated. Gentamicin and nafcillin therapy was begun. Four compartment fasciotomies of the right calf were performed. All muscles appeared viable. Gram stain of the edema fluid showed Gram-positive cocci in chains. Drains were placed but tissue was not debrided.

Leg edema receded but fever persisted during the first two hospital days. Tissue cultures grew GAS; blood cultures were negative. Antibiotics were narrowed to high dose penicillin G alone. On the second postoperative day the patient developed a scarlatiniform rash across his trunk with myalgias, abdominal pain, nausea and fever. On the following morning he had a sudden increase in erythema and edema of the right lower extremity extending onto the abdomen.

He was transferred to Children's Hospital. In transport he experienced hypotension and tachycardia, requiring fluid resuscitation and dobutamine infusion. Endotracheal intubation was performed for airway control and dopamine was added for persistent hypotension. Antibiotics were changed to clindamycin, ceftriaxone and penicillin. The areas of induration on the right thigh and anterior abdominal wall were

incised down to and including the muscle fascia. There was marked edema but no grossly visible soft tissue, fascial or muscle necrosis. A Gram-stained smear of the edema fluid showed multiple neutrophils with no organisms, and tissue debridement was considered unnecessary.

A similar regimen of HBO therapy was initiated but after the first treatment the induration extended to the abdomen and right foot. He returned to the operating room with repeat examination of the abdomen and full thickness incision of the induration of the right foot. No necrotic tissue was apparent and a Gram-stained smear of the edema fluid was unremarkable. Further HBO appeared to be temporally related to regression of the fasciitis rash by 2 to 3 cm circumferentially with each treatment. The surgical wounds were closed under minimal tension on Hospital Day 13, and he was discharged home 3 days later with good function.

RESULTS

The clinical presentations of 14 patients treated at Children's Hospital are summarized in Table 1. The 10 boys and 4 girls were treated from January, 1993, until May, 1995. Ages ranged from 6 months to 10 years (median, 4.0 years). The median duration of varicella exanthem before secondary symptoms was 3 days. The most common presenting symptoms of necrotizing fasciitis included erythema (71%), focal pain (79%), fever >38.5°C (85%) and localized tissue swelling (71%). Pain was often described as being out of proportion to other clinical findings. Secondary symptoms usually evolved in several hours, except in one patient (Patient 9) whose symptoms progressed for 48 hours. Affected anatomic sites are listed in Table 1. In the majority of patients no obviously superinfected pox lesions were found overlying the anatomic site of the fasciitis. Eight patients were initially evaluated and discharged before returning with advancing symptoms. Of these patients 7 received oral antibiotics with 5 diagnoses of cellulitis and 2 diagnoses of otitis media. Seven patients received analgesics.

The inpatient courses of the 14 patients treated are summarized in Table 2. Admission leukocyte counts ranged from 7300 to 27 900 cells/mm^3 with 15 to 61% band forms. All patients received parenteral antibiotics before surgery. Combination therapy including clindamycin (40 mg/kg/day divided every 8 hours) and a penicillin was ultimately used in each case. All patients underwent full thickness incision including the muscle fascia and debridement of all necrotic tissue. In patients with clinical symptoms consistent with a compartment syndrome, fasciotomies were performed but no patient had evidence of myonecrosis. Two patients (Patients 2 and 9) received repeat surgical exploration and debridement for advancing disease while receiving large dosage penicillin. Only nonpurulent edematous fluid was evident on repeat exploration.

All patients had positive tissue Gram-stained smears and culture for GAS. Only 2 patients had positive blood cultures; neither had received previous antibiotic therapy. Five patients developed hypotension, tachycardia and oliguria indicative of streptococcal toxic shock syndrome. These 5 patients were managed successfully with fluid and ionotropic support. Twelve patients were treated with adjunctive HBO therapy, ranging from 2 to 6 treatments (2.4 atmospheres for 2 hours) at 12-hour intervals. Of these 12 patients, 6 appeared subjectively to have regression of localized erythema and swelling in temporal association with HBO treatments. Two patients developed

TABLE 1. Prehospitalization course of 10 children with group A streptococcal necrotizing fasciitis complicating varicella

Patient	Date	Age	Sex	Site of Fasciitis	Duration of Varicella (Days)	Presenting Symptoms*	Evolution of Symptoms	Oral Antibiotics	Oral Analgesics
1	Dec. 1993	6 years	F	Thigh Abdomen	6	E, P	<12 hours	Cephalexin Acyclovir	Ibuprofen Acetaminophen
2	Feb. 1994	8 years	M	Calf Foot	4	S, P, F	<12 hours	None	Ibuprofen
3	March 1994	3 years	M	Calf Foot	2	E, S, P, F	<12 hours	TMP/SMX	Ibuprofen
4	April 1994	10 years	M	Calf Foot	2	E, S, P	1 day	Erythromycin Cephalexin	None
5	Dec. 1994	3 years	M	Abdomen	5	E, F	1 day	Cephadroxil	Acetaminophen
6	Dec. 1994	5 years	M	Thigh	3	E, P, F	<12 hours	None	Ibuprofen Acetaminophen
7	Jan. 1995	7 years	M	Axilla	4	E, S, P, F	1 day	Cefzil	Acetaminophen
8	Jan. 1995	6 months	F	Cheek	2	E, S, P, F	<3 hours	None	None
9	Jan. 1995	4 years	M	Thigh	2	S, P, F	1.5 days	None	Ibuprofen
10	Feb. 1995	1 year	M	Buttocks	5	E, F	<12 hours	Amoxicillin	None
11	April 1995	2 years	F	Shoulder	4	S, P, F	1 day	Cephalexin	None
12	April 1995	3 years	M	Axilla	4	S, P, F	<12 hours	None	None
13	April 1995	6 years	M	Neck	3	E, S, P, F	1 day	None	None
14	May 1995	8 months	F	Scalp	4	E, S, F	1 day	None	None

* Presenting symptoms.

E, erythema; S, swelling; P, pain; F, fever; TMP/SMX, trimethoprim/sulfamethoxazole.

TABLE 2. Inpatient course of 10 children with group A streptococcal necrotizing fasciitis complicating varicella

Patient	WBC (Bands)	Positive Cultures	TSS	Surgical Debridement	Antibiotics	HBO Treatment	Wound Closure (Days)	Hospital Stay (Days)
1	9900 (32)*	Tissue	+	Extensive, repeated	A/C/G	4	13	25 (4)†
2	9400 (61)	Tissue	+	Extensive, repeated	P/C/F	4	13	16 (7)
3	15 600 (43)	Tissue	+	Moderate	V/C/G	2	4	7 (3)
4	27 900 (14)	Tissue	+	Extensive	N/C/G	4	5	28 (4)
5	17 500 (17)	Tissue	–	Moderate	P/C/G	5	9	11 (4)
6	12 900 (46)	Tissue Blood	–	Extensive	P/C/G	6	6	9 (3)
7	13 000 (41)	Tissue	–	Moderate	P/C/G	0	5	6 (1)
8	19 800 (36)	Tissue	–	Tempered	P/C/G	5	13	15 (5)
9	20 900 (15)	Tissue Blood	–	Extensive	P/C	5	13	10 (3)
10	13 000 (ND)	Tissue	–	Moderate	A/C/G	0	7	9 (2)
11	16 100 (36)	Tissue	+	Extensive	N/C/G	4	9	13 (2)
12	21 700 (38)	Tissue	–	Moderate	C/G	2	7	9 (2)
13	7 300 (35)	Tissue	–	Moderate	N/C/G	3	7	9 (2)
14	9 200 (31)	Tissue	–	Moderate	N/C/G	3	3	6 (2)

* Numbers in parentheses, percent.

† Numbers in parentheses, days in ICU.

WBC, white blood cells; TSS, toxic shock syndrome; ICU, intensive care unit; A, ampicillin; G, gentamicin; F, ceftriaxone; C, clindamycin; P, penicillin; V, vancomycin; N, nafcillin; ND, not done.

complications of HBO treatment: one had a severe episode of bronchospasm requiring inhaled and parenteral beta-sympathomimetics and parenteral corticosteroids; the second child inadvertently extubated during transport from the chamber and the airway was immediately resecured.

All patients were admitted to the intensive care unit after surgery where the median stay was 3 days. Wounds were left open initially and delayed closure was performed from 4 to 13 days (median, 7 days). Two patients required skin grafting. Total duration of hospitalization ranged from 6 to 28 days (median, 10 days). One patient (Patient 6) was readmitted 10 days after discharge for wound infection and was successfully treated with antibiotics.

DISCUSSION

We present 14 patients with necrotizing fasciitis complicating primary varicella. Although the present series represents a retrospectively reviewed, uncontrolled population, the increase of necrotizing fasciitis and other invasive GAS disease,[1, 2, 12] as well as the importance of early recognition to improved outcome, warrant examination of the clinical features of this disease and the rationale behind existing therapies.

Streptococcal virulence factors. The pathophysiology of necrotizing fasciitis encompasses several phases: initiation of infection; dissection of tissue planes; intense inflammation; disruption of the blood supply; and direct cytotoxicity.[5, 6, 12, 13] A number of virulence factors contribute to the pathogenicity of invasive GAS.[7,12] M protein, a GAS surface antigen, confers antiphagocytic activity and permits initiation of infection in the absence of M type-specific antibodies.[2] In the recent resurgence of invasive GAS disease, M types 1 and 3 have been more frequently associated with invasive and fatal infections than other M types.[2, 7] There has been a concurrent shift in the production of GAS pyrogenic exotoxins with streptococcal pyrogenic exotoxin (SPE) A and SPE B more prevalent among invasive isolates.[1–3, 14, 15] Both toxins appear to mediate fever, tissue injury and toxic shock by activating host T cells, leading to production of the cytokines tumor necrosis factor alpha, interleukin 1-beta and interleukin 6.[16–18] Infections associated with the presence of SPE A are frequently severe, characterized by shock, tissue destruction and a scarlatiniform rash.[2] The production of protease by invasive GAS may be associated with the clinical syndrome of necrotizing fasciitis.[7]

GAS necrotizing fasciitis and varicella. The basis for the association between GAS necrotizing fasciitis and primary varicella has yet to be fully elucidated. The rash of varicella consists of full thickness dermal lesions[19] and may represent a portal of entry for the GAS residing on the skin. Alternatively varicella infection may produce a transient, selective immunosuppression *vs.* GAS, but this hypothesis has not been examined.

Necrotizing fasciitis remains difficult to diagnose in its early stages when it is often confused with cellulitis and when it is most amenable to treatment.[5, 6, 13] In this study seven patients experienced delays in diagnosis because of nonspecific early clinical findings as well as an underappreciation of this disease and its association with varicella. Radiographic studies frequently do not elucidate the severity of the infection. A recent report suggests that magnetic resonance imaging may help delineate the extent of soft tissue involvement in necrotizing fasciitis and thus serve as a useful

diagnostic tool.[20] However, such extensive diagnostic evaluations should not delay surgical intervention, which remains the definitive approach to both diagnosis and treatment.

Our experience indicates that any of several signs or symptoms should alert the physician to the possibility of invasive GAS superinfection of varicella: (1) high fever after the first 48–72 hours; (2) localized swelling, erythema, induration, *peau d'orange* appearance or warmth; (3) pain, often out of proportion to other clinical findings; (4) refusal to bear weight or move an extremity; (5) scarlatiniform eruption; (6) toxic or lethargic appearance; (7) hypotension; or (8) tachycardia. Suspicion of necrotizing fasciitis must prompt immediate surgical consultation inasmuch as the prognosis depends largely on the rapidity of recognition and initiation of appropriate surgical and antibiotic therapy.

Surgical intervention. Definitive diagnosis and therapy of necrotizing fasciitis are made surgically.[6, 8] The use of frozen section biopsy has decreased the time to diagnosis and improved survival,[8] although diagnosis is often clinically apparent at the time of surgery. The presence of neutrophilic infiltrates on frozen section biopsy of wound margins may aid in establishing the margins of debridement.[6] Frozen section biopsy was used in Patient 1 after admission to the pediatric intensive care unit in order to examine an area of advancing erythema, but no neutrophilic infiltrates were found. A positive biopsy would have been an indication for further surgical exploration.

The surgical procedure involves full thickness incision of all indurated areas, down to and including the muscle fascia, in order to examine all tissue planes and the underlying muscle. Compartment fasciotomies are required in patients when preoperative concerns of compartment syndrome exist. Wounds should then be explored along superficial fascial planes and necrotic tissue should be debrided as necessary. The extent of debridement can be judged either by observation and the presence of bleeding or by use of frozen section biopsy. All patients require supportive care in the pediatric intensive care unit postoperatively.

Antibiotic therapy. The extremely rapid course of infection combined with difficulties in initial diagnosis contributes to the continued high morbidity and mortality of GAS necrotizing fasciitis despite antibiotic therapy. Although GAS strains remain universally sensitive to penicillin (PCN), Eagle[21] showed that when the organism is present in concentrations of $>10^7$ organisms/mm^3, PCN may become less effective, the so-called "inoculum effect."[22] Large inocula of GAS may reach stationary growth phase rapidly and express decreased levels of penicillin-binding proteins.[22] Such large concentrations are probably encountered clinically only in abscess cavities, necrotizing fasciitis, myositis and overwhelming sepsis.[12]

In contrast to PCN clindamycin may possess certain theoretical advantages in overwhelming GAS infections.[22] Clindamycin exerts its antibacterial effect by inhibiting bacterial protein synthesis. It does not require cell wall penicillin-binding proteins and is not subject to the inoculum effect.[23] Furthermore inhibition of protein synthesis by clindamycin could block production of M proteins, SPE and protease implicated in septic shock and tissue injury of GAS necrotizing fasciitis. In a mouse model of GAS myositis, Stevens et al.[22] demonstrated that 100% of mice died when PCN therapy was initiated 2 hours after bacterial inoculation, whereas >80% of mice survived when clindamycin monotherapy was used, even after a 16-hour delay. Whether these observations apply to human GAS disease is unknown.

Although all of our patients received clindamycin as part of their postoperative antibiotic regimen, its precise contribution to their recovery cannot be quantified. On the basis of experimental data and the favorable outcome of our 14 patients, we recommend consideration of clindamycin in the antibiotic treatment of necrotizing fasciitis. The efficacy of any antibiotic regimen, however, depends on adequate surgical therapy.

HBO. HBO has been used as an adjunct in the treatment of necrotizing fasciitis of anaerobic, mixed and unknown bacteriologic etiologies.[6, 9–11] Riseman et al.[10] retrospectively described 29 adults with necrotizing fasciitis using historical controls. The HBO-treated patients were reported to be more seriously ill at the time of presentation, but the mortality rate (23% *vs.* 66%) and the need for repeated surgical debridement (1.16 *vs.* 3.25) were significantly reduced compared with the control group. Mortality was also lower for patients with aerobic infections among the HBO-treated group compared with controls. Other uncontrolled studies demonstrated similar favorable outcomes.[9, 11]

The apparent benefit of HBO therapy in 6 of 12 patients in this study is subjective. A theoretical foundation for the action of HBO therapy in GAS necrotizing fasciitis may reside in improving host leukocyte response by increasing oxygenation of compromised tissue at the site of infection.[24–27] Increased tissue oxygenation may also assist wound healing[27–29] by augmenting collagen deposition, angiogenesis and re-epithelialization.[30, 31]

Importantly two patients developed complications resulting from the HBO treatments, including an inadvertent extubation during transport from the chamber and one episode of severe bronchospasm. Both compli-

cations were treated successfully. Furthermore HBO is not available at all institutions. Thus any potential benefit of HBO therapy must be weighed against the known risks, and its use should be individualized based on patient acuity and transport feasibility. Prospective studies of supportive surgical and antibiotic treatment with and without HBO in patients with necrotizing fasciitis are warranted.

Nonsteroidal antiinflammatory agents (NSAIDS). There have been several reports of an association between nonsteroidal antiinflammatory medications and the subsequent development of fulminant necrotizing fasciitis.[32–34] In those reports NSAIDS were administered immediately after diagnosis, with subsequent marked acceleration of the disease process. Animal models have demonstrated impaired granulocyte function including chemotaxis, phagocytosis and bactericidal activity by NSAIDS.[33] NSAIDs may simply mask signs of disease progression such as pain, fever and local inflammation and contribute to delays in diagnosis. Five of our patients received ibuprofen and were discharged at the time of their first presentation with GAS disease. Consequently it may be prudent to limit the use of NSAIDS for local complications of varicella.

We present 14 children with necrotizing fasciitis after primary varicella infection. All 14 patients received parenteral antibiotics, surgical debridement and intensive care and eight had adjunctive HBO therapy. Outcome was excellent despite initial delays of 12 to 72 hours from onset of localizing symptoms to diagnosis and referral in 8 patients. It is difficult to assess the relative contributions of each therapeutic modality. Surgery remains the cornerstone of both diagnosis and treatment. Clindamycin and HBO therapy may have a role in this disease, but further study is required. Primary care providers must be aware of the early clinical signs of GAS necrotizing fasciitis and its association with primary varicella to limit morbidity and mortality from this dangerous infection.

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Tumor necrosis factor concentrations in hemolytic uremic syndrome patients and children with bloody diarrhea in Argentina

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Hemolytic uremic syndrome (HUS) is thought to be a vascular endothelial injury disease. The mechanism of injury is unknown although verocytotoxins (Shiga-like toxins (SLTs)) are known to be associated with it. Recent evidence suggests that *in vitro* treatment of some endothelial cells with tumor necrosis factor alpha (TNF-alpha) dramatically increases their susceptibility to SLTs. We studied 25 children with HUS, 63 children with SLT-positive bloody diarrhea, 62 children with bloody diarrhea not associated with SLTs and 39 children admitted for elective surgery, included as an age- and season-matched control group. The TNF-alpha concentrations were found to be significantly elevated in children with HUS (range, 1 to 95 pg/ml; geometric mean, 32.2 pg/ml) compared with the healthy controls (range, 0 to 53 pg/ml; mean, 12.5 pg/ml; $P < 0.001$). Because it is hypothesized that TNF-alpha elevation might precede development of HUS, we also studied children with bloody diarrhea. The TNF-alpha serum concentrations were significantly higher during the first 10 days after onset of bloody diarrhea than after the first 10 days ($P < 0.02$). Such elevation could be associated with vascular endothelial glycolipid receptor up-regulation and increased susceptibility to the effects of SLTs.

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INTRODUCTION

Hemolytic uremic syndrome (HUS) is characterized by microangiopathic hemolytic anemia, acute renal failure and thrombocytopenia. This syndrome occurs typically after an episode of bloody diarrhea.[1] *Shigella dysenteriae* 1 and enterohemorrhagic *Escherichia coli* are associated with both bloody diarrhea and HUS. The virulence of these organisms has been linked to the production of Shiga-like toxins (SLT-I and SLT-II). These toxins are also called verotoxins or verocytotoxins.[2, 3] Enterohemorrhagic *E. coli* organisms are known to colonize the gastrointestinal tract and produce SLTs detectable in the stool. Because enterohemorrhagic *E. coli* organisms are not classically invasive, SLTs must translocate from the lumen to the tissues, but the mechanism is unknown. SLTs are composed of subunits: one catalytic A subunit involved in the inhibition of protein synthesis; and five identical B subunits that spontaneously assemble into pentamers and bind to cell surface glycolipid (globotriaosylceramide (Gb_3)).[4, 5]