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#### [Infection]

# Orthopaedic Manifestations of Invasive Group A Streptococcal Infections Complicating Primary Varicella

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# **Abstract**

Summary: The incidence of invasive group A streptococcal (GAS) infections in primary varicella appears to be increasing. GAS infections complicating varicella range from cellulitis, abscess, and septic arthritis to life-threatening necrotizing fasciitis and pyomyositis in association with GAS toxic shock syndrome (TSS). Four patients admitted in 1 year to the Children's Hospital and Medical Center in Seattle, whose care included evaluation and treatment by the Orthopaedic service, are presented to illustrate this spectrum. Three had a delay in diagnosis, including discharge from previous emergency department visits. One patient with polyarticular septic arthritis was treated with diagnostic aspiration and intravenous antibiotics. The remainder required urgent surgical debridement for treatment of deep infection. Patients with necrotizing fasciitis or pyomyositis had life-threatening complications of TSS, including hypotension, adult respiratory distress syndrome (ARDS), coagulopathy, and acute renal failure. These patients required aggressive fluid resuscitation and prolonged intensive care unit support. Diagnostic imaging studies were obtained in one patient with necrotizing pyomyositis but may have served only to delay definitive treatment. Recognition of the potential for secondary GAS infections and a high index of suspicion for the presence of necrotizing soft-tissue infection are essential in the evaluation of any child with fever and localized extremity pain with varicella.

Group A Streptococcus (GAS) is responsible for a wide range of soft-tissue infections, from oropharyngeal and skin infections (pharyngitis cellulitis, erysipelas) to necrotizing fasciitis and myositis. Invasive GAS may affect people of all ages (17). Recent reports in the pediatric infectious disease and emergency medicine literature suggested an increasing incidence of severe, frequently lifethreatening, soft-tissue infections caused by GAS complicating varicella infection in children (2,3,5,19,21,32). In the last 12 months, four patients have been admitted to the Children's Hospital and Medical Center in Seattle with an invasive GAS infection of one or multiple extremities with various stages of varicella infection. Delay in diagnosis occurred in three of these patients. Each had complaints of fever and extremity pain, was discharged home, and later returned with advancing soft-tissue infection.

Although postvaricella GAS osteomyelitis (14,21) and septic arthritis (11,22) have been reported, we were unable to find any reports of postvaricella GAS necrotizing soft-tissue infections or GAS toxic shock syndrome (TSS) in the orthopaedic literature. These entities have significant orthopaedic implications and appear to be increasing in frequency.

A cluster of four pediatric cases from 1 year are presented. They represent a spectrum of invasive postvaricella GAS infections. Early suspicion for the possibility of this association is urged. The distinction is made between necrotizing pyomyositis and less severe forms of bacterial myositis, and the potential severity of associated GAS toxic shock syndrome is emphasized.

## **CASE REPORTS**

Case 1: Multifocal septic arthritis

A 14-month-old boy developed erythema on the dorsal aspect of his left foot 4 days after the onset of varicella and subsequently refused to bear weight on his left lower extremity (Table 1: patient summary). He was seen by his primary physician the following day; the area of erythema was noted and marked, but no treatment was prescribed. One day later, with persistent left foot symptoms, he became febrile to 104°F and developed pain in his right elbow and left knee. He was seen in our emergency department (ED) the next day with a temperature of 38.9°C, heart rate of 160 beats/min, and blood pressure of 101/68 mm Hg. Physical examination revealed diffuse dry skin lesions of varicella, many with surrounding erythema. There was moderate swelling with acute tenderness about the left ankle, left knee, and right elbow; a minimal knee effusion and moderate ankle effusion were noted. White blood cell count (WBC) was 16,600/mm<sup>3</sup>; erythrocyte sedimentation rate (ESR) was 115 mm/h; and C-reactive protein (CRP) was 5.8 mg/dl. Turbid fluid (1 ml) was aspirated from the left ankle, blood for cultures was drawn, and the patient was admitted for i.v. antibiotics (nafcillin). A bone scan was obtained and revealed significantly increased blood pool in the left ankle and right elbow, with moderately increased uptake about the left knee (Fig. 1). The patient improved rapidly over a 24-h period, with increased joint motion and decreased focal tenderness. Blood and joint aspirate cultures grew GAS. Antibiotic coverage was changed to penicillin. The patient gradually resumed weight bearing on the left lower extremity. He remained afebrile and was discharged 6 days after admission with oral penicillin

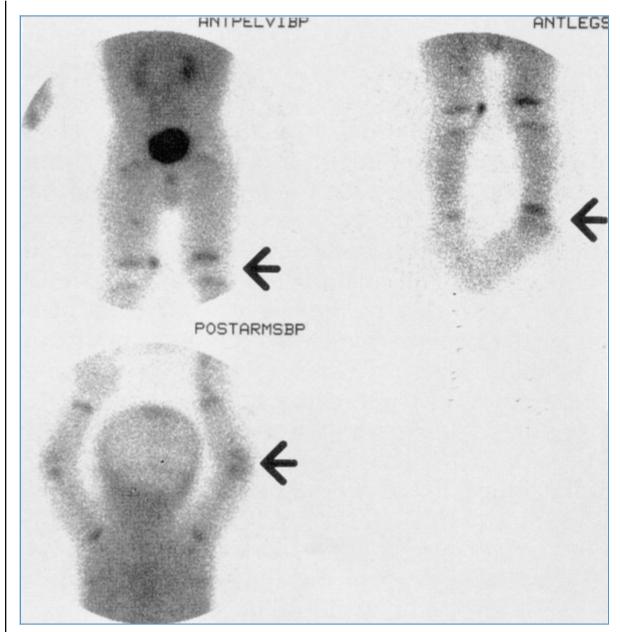
with a diagnosis of GAS septic polyarthritis complicating varicella. Two weeks later, he returned to the clinic with persistent swelling and limited motion of his right elbow. The elbow was aspirated, producing scant fluid and negative cultures. Periosteal elevation noted on lateral elbow radiographs was thought to be consistent with distal humerus osteomyelitis. His ESR was 91 mm/h. He was treated for presumptive distal humeral osteomyelitis with 2 days of i.v. antibiotics in the hospital and 6 weeks of home i.v. antibiotics. He responded quickly to antibiotic therapy, with resumption of free elbow range of motion after 2 days. At the end of 6 weeks' treatment, his ESR was 15 mm/h, and examination was notable for painless passive range of motion of all his extremities, including his right elbow. Long-term consequences of multifocal septic arthritis and distal humeral osteomyelitis remain to be seen.

Case no.	Age (yr)	Sex	Initial Dx	Final Dx	TSS?	Delay in Dx (hr)	Hospital days	Clinical findings
1	1.2	M	_	Septic arthritis	No	36	6	_
2	10	M	Cellulitis	Nec. fasciitis	Yes	72	10	Hypotension, ARDS
3	5	F	Septic arthritis	Pyomyositis	No	_	5	_
4	5	F	Abscess	Nec. pyomyositis	Yes	48	25	Hypotension, ARDS, coagulopathy, ARF

Dx, diagnosis; Nec., necrotizing; ARDS, adult respiratory distress syndrome; ARF, acute renal failure; TSS, toxic shock syndrome.

**TABLE 1.** Patient summary

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**FIG. 1.** Acute-phase bone scan revealing increased blood pool in left ankle and right elbow; moderate increase about the left knee. Arrows, pathology.

Case 2: Necrotizing fasciitis

A previously healthy 10-year-old boy developed varicella with cutaneous and oral lesions. On the second day of his exanthem, he complained of left leg swelling and pain with weight bearing. A diffuse erythematous rash over his torso and extremities appeared the following day. He was seen by his primary physician 5 days after the onset of varicella for fever and increased swelling of the left leg. Oral antibiotics were prescribed for suspected streptococcal cellulitis. The following day, he returned to his primary physician with advancing proximal swelling. A change in oral antibiotics was prescribed, but the erythema and swelling continued to advance. On the seventh day after the onset of varicella, the patient was transferred to Children's Hospital.

In our ED, his temperature was 37.8°C., blood pressure (BP), 111/64 mm Hg, and pulse 132 beats/min. He was noted to have a swollen, indurated, and tender left calf and foot with knee and ankle range of motion limited by pain. WBC was 27,900/mm<sup>3</sup>, and ESR, 68 mm/h. Thrombin time was 29 s, and fibrinogen split products were elevated. BUN and creatinine were within normal range. Volume resuscitation was initiated, blood cultures drawn, nafcillin, gentamicin, and clindamycin begun, and he was taken directly to the operating room where four compartment fasciotomies were performed. Necrotic skin, subcutaneous tissues, and fascia were debrided. The extent of the debridement was aided by frozen-section biopsy, which showed neutrophilic infiltrates. Underlying muscle was viable. Wound cultures grew GAS, but blood cultures remained negative. En route to another institution for hyperbaric oxygen treatment, he became hypotensive, requiring inotropic support and intubation. Ultimately, he received four hyperbaric oxygen treatments. He extubated without complications and was transferred from the intensive care unit (ICU) on the third hospital day. Fasciotomy wounds closed without requiring skin grafts, and he was discharged home with no notable loss of lower extremity function to complete 2 weeks of i.v. antibiotics.

#### Case 3: Pyomyositis

A 5-year-old, left-hand-dominant girl was seen in an outside ED 10 days after onset of varicella lesions complaining of 4 days of increasing left shoulder girdle pain, with fever to 104°F. On examination, she had swelling about her shoulder, moderate erythema, and local tenderness. Her WBC was 16,000/mm³, and ESR, 93 mm/h. Under general anesthesia, her glenohumeral joint and proximal humeral metaphysis were aspirated, and varicella lesions cultured. Gram stain of the attempted glenohumeral aspirate, via a posterior approach, revealed gram-positive cocci, and the patient was transferred to our institution for further care.

In our ED, she remained febrile to 102°F, with BP of 110/60 mmHg and HR of 100 beats/min. She had dry crusted varicella lesions diffusely and was unwilling actively to move her left arm or shoulder. Her examination was notable for maximal tenderness and marked localized swelling posteriorly over the lateral scapula, with minimal anterior shoulder or proximal humeral tenderness. Passive glenohumeral motion was not particularly painful, with little guarding.

Blood for cultures was drawn, intravenous antibiotics begun, and the patient admitted with a diagnosis of possible parascapular abscess. A computed tomography (CT) scan demonstrated fluid collections both anterior and posterior to the scapula, blurring of fat planes, and induration of the subcutaneous fat (Fig. 2). She was taken to the operating room that night for incision and drainage of 30 ml of purulent fluid from a

left parascapular abscess cavity within the substance of the infraspinatus and tracking anteriorly to involve the subscapularis as well. No significant myonecrosis was evident. The wound was partially closed over drains. She had an unremarkable postoperative course, with gradual healing of her surgical wounds. Wound, throat, and varicella lesion cultures all ultimately were positive for GAS, although blood cultures remained negative. After 3 days of intravenous antibiotics, she completed a 6-week course of oral clindamycin. Eight months later, her range of motion is full, and there is no evidence of growth arrest, osteomyelitis, or other postinfection sequelae.

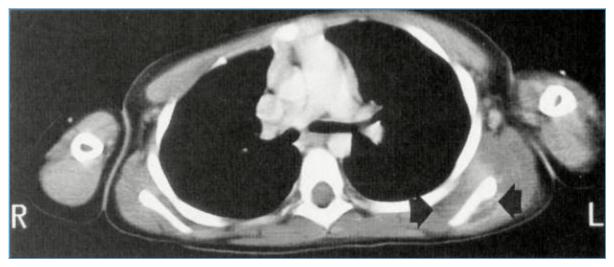


FIG. 2. Coronal CT through mid/inferior scapular level; heterogeneous signal is present both anterior and posterior to the left scapula.

## Case 4: Necrotizing pyomyositis

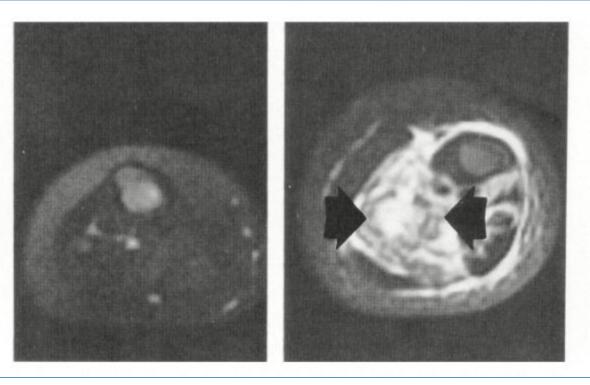
A 5-year-old girl was seen in our ED complaining of left heel pain 1 week after the onset of varicella lesions. There was no history of trauma. No focal erythema was noted on examination. She was evaluated and discharged with a diagnosis of Achilles tenosynovitis. She was seen 2 days later by her pediatrician because of worsening pain in the left heel that extended proximally to involve the posterior aspect of her calf. She was refusing to bear weight. Her physician noted lethargy and decreased appetite. Blood was drawn for a CBC and cultures, and the child was sent back to the ED.

Her temperature in the ED was 37.4°C. She was lethargic but arousable, following commands. Blood pressure measured 135/85 mm Hg, and HR was 136 beats/min. Dry crusted varicella skin lesions were noted diffusely. Her left lower extremity examination was notable for painless hip and knee range of motion. Her leg was swollen with proximal posterior tenderness. She would actively flex and extend all toes and plantarflex her ankle. She denied pain with passive flexion or extension of her toes but had severe pain with passive dorsiflexion of the ankle. There was no erythema or induration of the skin or any bullus formation. There was tender inguinal adenopathy without lymphangitis. Her WBC was 2,600/mm³; ESR, 45 mm/h; and CRP, 38 mg/dl. Compartment pressures measured 26 mm Hg in the anterior and lateral compartments, 32 mm Hg in the deep posterior compartments, and 40 mm Hg in the superficial posterior compartment. Plain radiographs showed soft-tissue swelling.

The patient was thought to have a deep infection in her posterior leg. She was admitted to the hospital taking broad-spectrum intravenous antibiotics. An emergency magnetic resonance imaging (MRI) study was obtained, which revealed heterogeneous abnormal signals in her superficial posterior compartment involving the entire soleus and a large portion of the lateral gastrocnemius. There was also remarkable signal abnormality in her deep posterior compartment and her distal medial thigh (Figs. 3 and 4). There was no focal fluid collection to suggest abscess.



**FIG. 3.** Coronal STIR MRI of left leg. Note heterogeneous signal abnormality in soleus and deep posterior compartment musculature with relative sparing of medial gastrocnemius border. No focal fluid collection is seen.



**FIG. 4.** Transverse (axial) T2-weighted MRI through proximal leg. Moderate fascial edema is noted diffusely, with marked signal abnormality in soleus and deep posterior compartment. The medial gastrocnemius is spared; the lateral gastrocnemius moderately involved.

Blood cultures previously drawn in the physician's office were reported to be positive for *Streptococcus* organisms. As plans were made to take the patient to the operating room, she developed profound bradycardia and hypotension. Cardiopulmonary resuscitation was initiated, and the patient was intubated and volume resuscitated. Once stabilized, she was taken directly to the operating room for exploration of her left leg. Four compartment fasciotomies were performed through medial and lateral incisions. Findings included generalized liquefaction necrosis of the soleus and a significant portion of the lateral head of the gastrocnemius. These were radically debrided. The medial gastrocnemius was contractile and appeared uninvolved. The deep posterior-, anterior-, and lateral-compartment musculature appeared relatively healthy. The fascia and overlying subcutaneous tissue and skin appeared grossly normal, but samples were sent for microscopic examination.

The medial aspect of the distal thigh was explored as well, with findings of muscle edema but no myonecrosis. The surgical wounds were left open. The patient was transferred directly to the ICU, where inotropic support and massive fluid resuscitation were required. She developed adult respiratory distress syndrome (ARDS), requiring prolonged ventilatory support, and she became coagulopathic. Acute renal failure responded to fluid resuscitation. Antibiotic coverage, which included penicillin and clindamycin, was initially directed by the blood cultures and soon after by the deep cultures of all excised muscle, which were positive for GAS. The child was transferred to a nearby institution early in her ICU course for a hyperbaric oxygen treatment, but her hemodynamic instability did not allow subsequent treatments. She returned to the operating room for irrigation and further debridement of her wounds on hospital days 6, 9, and 15. Progressive necrosis of her tibialis posterior and flexor hallucis muscles, as well as small portions of her peroneus longus

muscle, were identified. These were debrided. Although there was no evidence of persistent deep infection at the time of these debridements, the patient remained febrile to >39.6°C. Her posterior tibial artery and veins were noted to be thrombosed throughout the length of her fasciotomy wound, and these were excised because of concerns about septic thrombosis. Repeated plain radiographs of her tibia and fibula revealed a patchy lucency in the distal tibial metaphysis. A gallium scan revealed increased uptake in a corresponding location. She returned to the operating room for incision and drainage of her distal tibia. Although no frank purulence was encountered, and intraoperative cultures were negative, she defervesced and remained afebrile thereafter. Delayed primary closure of her medial wounds was performed at day 19 after the index procedure. The lateral fasciotomy wound required a split-thickness skin graft. The child was extubated without complication and had an uneventful recovery after a prolonged ICU course.

More than 2 months have passed since this nearly catastrophic event. The child used an ankle-foot orthosis initially but now chooses to be brace free. She has active ankle dorsiflexion and weak but present plantarflexion. Her foot is plantigrade during gait, and she walks with a painless mild limp. Sensation is intact on all aspects of her foot. Her long-term functional deficit and risk for progressive foot deformity are unknown but anticipated.

#### DISCUSSION

Varicella is a common viral infection that generally follows a benign, self-limited course. Complications do occur, however. It was reported in the past decade that varicella resulted in >6,000 hospital admissions per year in the United States (15). Serious complications including soft-tissue infections, meningitis, pneumonia, sepsis, and death can occur (13,20). Recently an association between varicella and severe soft-tissue infection due to GAS has been reported (2,5,6,24,28,39). It has been postulated that the exanthem of varicella, known to consist of full-thickness dermal lesions, may represent a ready portal of entry for GAS residing on skin.

The patients in this article represent a spectrum of invasive GAS musculoskeletal infections that may complicate varicella and that the orthopaedic surgeon may be asked to evaluate and treat. These serious infections must be distinguished clinically from more common local complications such as superficial cellulitis. When the GAS organism has gained access to the bloodstream, it is evident that invasion of synovium (patient 1), bone (patient 1), fascial tissues (patient 2), or muscle (patients 3 and 4) is possible.

GAS septic arthritis complicating primary varicella has been reported elsewhere (4,10,11,30). Glass et al. (11) reported GAS monoarticular knee septic arthritis in a 21-year-old man, who was treated with repeated arthrocentesis and i.v. antibiotics. Our patient 1 underwent diagnostic aspiration followed by i.v. antibiotic treatment for polyarticular involvement, an approach supported in joints other than the hip when clinical improvement is seen (16,37). Distal humerus osteomyelitis developed, however, and complicated his recovery. GAS osteomyelitis has been reported in other children with primary varicella (14,21). Because (a) osteomyelitis is likely to require longer courses of parenteral antibiotics to achieve sterilization and (b) the radiographic diagnosis of osteomyelitis may not be possible at first presentation, careful follow-up examination is required before and after the decision to switch to oral antibiotics therapy.

GAS necrotizing fasciitis is a well-documented complication of primary varicella (8,21,24,31) and has been the most common manifestation of invasive GAS disease in children at our institution (3). The diagnosis of necrotizing fasciitis is made challenging by the nonspecific nature of early clinical findings: fever, pain, and erythema. Pain may significantly precede the development of localized signs of inflammation, and the site of fasciitis may be distant from any remaining varicella skin lesions (3). Diagnosis and primary therapy is achieved through surgical exploration (27,32), with examination of all tissue planes and thorough debridement of necrotic tissue. Frozen-section biopsy may aid in determining the extent of debridement required (32). Compartment fasciotomies should be performed when clinically indicated (3).

Pyomyositis is a fairly common and well-recognized entity in tropical climates. The most common pathogen is *Staphylococcus aureus* (5,7). Pyomyositis in more temperature climates is rare, although it may be more common in children in these locations (12). Pyomyositis involving the psoas, infraspinatus, tibialis anterior, and hip adductors was recently reported in five children (25). All patients were admitted to the hospital with a diagnosis other than pyomyositis. Four of the five patients required surgical drainage. *S. aureus* was cultured in two patients, *Streptococcus pneumoniae* in one and *Streptococcus pyogenes* (GAS) in another. Abscess formation was a constant surgical finding. One patient, treated with antibiotics only, was thought to have early pyomyositis without abscess formation. No organism was isolated in this patient. One patient appeared remarkably similar to our patient 3, with pyomyositis of the infraspinatus caused by GAS. CT scan also was useful in making the diagnosis in that case, although the authors suggested that MRI is a more useful tool in identifying the presence or absence of joint effusions and therefore can more readily rule out septic arthritis. In our patient 3, the extensive evaluation to rule out more common childhood infectious etiologies (i.e., septic glenohumeral arthritis and proximal humeral osteomyelitis) emphasizes both the need for meticulous physical examination to localize sites of infection and the potential diversity of GAS infections in this setting.

Pyomyositis appears to be a rare manifestation of invasive GAS. Adams et al. (1) reviewed 21 cases reported in the literature between 1930 and 1985. Nather et al. (23) described two cases of streptococcal pyomyositis, one in an 11-year-old boy with extensive myonecrosis. They emphasized the importance of discriminating between (a) bacterial myositis, which may respond well to simple incision and drainage followed by intravenous antibiotics, and (b) necrotizing pyomyositis, characterized by massive muscle necrosis requiring radical surgical debridement. Patients 3 and 4 described herein illustrate this distinction.

Distinguishing necrotizing fasciitis (patient 2) from pyomyositis (patients 3 and 4) may not be possible preoperatively. Elevated or increasing serum creatine kinase levels may be seen in both conditions (33,35). Late in the clinical course, patients with necrotizing fasciitis will typically develop overlying skin changes such as erythema, bullae, induration, crepitation, or epidermal necrosis (24,33,39), whereas those with isolated pyomyositis have been reported to have minimal or no skin changes (1,24,36). Optimal management of either form of invasive GAS disease requires recognition and aggressive surgical intervention before the process extends into more superficial tissue planes.

The utility of obtaining various imaging studies in the clinical setting of GAS necrotizing fasciitis or pyomyositis requires consideration. Patient 3, who was hemodynamically stable at presentation, benefited from CT imaging to confirm intramuscular abscess and plan surgical drainage. Distinction from the more common septic arthritis or osteomyelitis may likewise have been aided, although her physical examination was suggestive as well. Patient 4, who was initially seen with lethargy and tachycardia, underwent an MRI scan that documented abnormalities, including infection of the calf muscle, but had a rapid deterioration and cardiopulmonary arrest before surgical intervention. Although MRI may be a useful diagnostic aid in early pyomyositis (25) and necrotizing fasciitis (39), imaging of the seriously ill patient will serve only to delay definitive surgical diagnosis and therapy. As a result, we have adopted a high index of suspicion of invasive GAS disease in children with varicella and clinical signs of localized soft-tissue infection; we favor immediate surgical exploration in any patient with evidence of systemic toxicity.

Intravenous antibiotic therapy is a second essential component of the treatment of invasive GAS complications of varicella. GAS remains universally sensitive to penicillin; however, treatment failures may occur in overwhelming infections such as necrotizing fasciitis or pyomyositis (33). This is perhaps a result of the slow growth of GAS in large abscess cavities, with resultant decreased efficacy of cell wall-active agents such as penicillin, the so-called "inoculum effect" (34). Ribosomally active agents such as clindamycin are not subject to the inoculum effect and may have the added benefit of inhibiting bacterial protein synthesis and toxin production (33,34). Currently we employ combination antibiotic therapy, including clindamycin and oxacillin or nafcillin, pending surgical drainage and debridement, stabilization of the patient, and definitive identification of the organism.

We and others have used postoperative hyperbaric oxygen therapy in patients with GAS necrotizing fasciitis, with subjective clinical benefit in some recipients (3,26). Because GAS is an aerobic organism, it is likely that any beneficial effect is mediated through improved oxygenation in vascularly compromised tissues and possible enhancement of host phagocytic function (18,19). Any potential benefit of hyperbaric oxygen treatment must be weighted against the hazards of transport to and from the chamber in critically ill patients.

In adult patients, GAS necrotizing soft-tissue infections are typically accompanied by severe streptococcal TSS (38), with mortality of 20-50% in necrotizing fasciitis and 80-100% in pyomyositis (33). Shulman (29) provided a distinction between invasive group A streptococcal infection with bacteremia and streptococcal TSS. The Working Group on Severe Streptococcal Infections (40) formally defined the diagnosis of GAS TSS as the occurrence of shock and multiorgan system failure early in the course of infection. The criteria for this diagnosis include isolating group A *Streptococcus*, hypotension, and organ system involvement with at least

two of the following: renal impairment, coagulopathy, ARDS, liver involvement, and soft-tissue necrosis. It is notable that extremity pain has been reported to be the most common initial symptom of streptococcal TSS in one series (35). Patient 2 manifested hypotension, tachycardia, and oliguria, suggestive of a streptococcal toxin-mediated process, and exhibited a scarlet fever-like rash known to be associated with streptococcal pyrogenic exotoxin A. Patient 4 exhibited full-blown TSS with multiple organ involvement: refractory hypotension, myocardial dysfunction, acute renal insufficiency, ARDS, and pronounced coagulopathy. It has been suggested that the streptococcal pyrogenic exotoxins and other streptococcal virulence factors (e.g., M protein) may act as superantigens, initiating a host response with massive cytokine release and consequent tissue injury (9,22).

In summary, children with varicella are at risk for a variety of invasive GAS musculoskeletal infections. Synovium, bone, fascia, and muscle may be involved. These infections have significant potential morbidity and may be complicated by the development of streptococcal TSS. The risk of TSS with invasive GAS disease mandates careful monitoring of all patients, fluid and inotropic support, and intensive perioperative supportive care. The prognosis of necrotizing fascial and muscle GAS infections depends on the rapidity of disease recognition and institution of surgical therapy. Orthopaedic surgeons should be aware of the association of GAS musculoskeletal infection with varicella and the importance of prompt, aggressive intervention.

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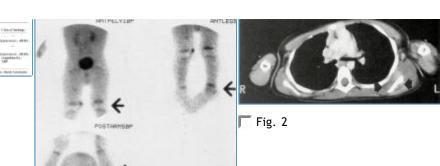
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Key Words: Group A Streptococcus; Necrotizing fasciitis; Pyomyositis; Septic arthritis; Toxic shock

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Table 1



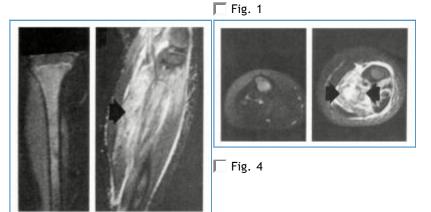


Fig. 3

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