Epidemiology and Outcome of Necrotizing Fasciitis in Children: An Active Surveillance Study of the Canadian Paediatric Surveillance Program

IHUOMA ENELI, MD, MS, AND H. DELE DAVIES, MD, MS

Objective To describe the epidemiology, management, and outcome of pediatric necrotizing fasciitis (NF) in Canada before full implementation of varicella immunization programs.

Study design This was a prospective cohort study of all children under age 16 years identified by the Canadian Paediatric Surveillance Program (CPSP).

Results Between November 1, 2001 and October 31, 2003, 36 NF cases were identified (mean age, 5.9 ± 5 years). Group A streptococcus (GAS)-related and non–GAS-related NF accounted for 2.12 and 0.81 cases per million children, respectively. The annual incidence was substantially higher in children under age 5 years (5.9 vs 1.8 per million; $P = .0002$). Males over age 1 year had the highest disease burden, with 12 cases per million, versus 3.2 cases per million for females under age 1 year ($P < .0001$). Most (15/26; 58%) GAS-related cases were associated with varicella. Complications occurred in 29 children (78%), and 2 children (5.4%) died.

Conclusion In the prevaccine era, NF occurred most commonly in Canadian children under age 5 years, with a peak incidence in males under age 1 year. There is substantial associated morbidity and about 5% mortality. The data provide baseline incidence of disease and a surveillance mechanism for NF after the implementation of publicly funded varicella immunization programs in Canada. *(J Pediatr 2007;151:79-84)*

Necrotizing fasciitis (NF) is a serious infection involving the subcutaneous tissue, fascia, and fat, with substantial morbidity and mortality.[1] NF may be classified into 2 types based on the causative organism. The first type includes those cases due to mixed infection from anerobes, most commonly *Bacteroides* and *Peptostreptococcus* species, facultative anaerobes such as non-group A [beta]-hemolytic streptococci, and *Escherichia coli*, *Enterobacter* species, *Klebsiella*, and *Proteus* species.[2] The other type of NF is caused by invasive group A streptococcus (GAS).[3] NF occurs at a higher frequency in patients with chronic disease, after varicella infection, possibly in association with use of nonsteroidal anti-inflammatory drugs (NSAIDs), and in patients with a history of recent surgery or trauma.[1,3-9]

The last 2 decades have brought an increase in the number of invasive GAS infections, including NF.[5,10,11] Some studies have focused on an altered virulence of the bacteria to explain the resurgence, identifying an association between M1 and M3 strains and invasive disease.[7-10]

Although there are many case reports and case series of NF,[2,4,12-17] there are no population-based studies of incidence involving primarily children. Population-based epidemiologic data for NF in children are needed to guide and monitor prevention programs, clinical recognition, and management. Using a national population-based, active surveillance system, we describe the epidemiology, management, and outcome of NF in Canada and compare epidemiologic features of GAS-related and non–GAS–related NF.

METHODS

Between November 1, 2001 and October 31, 2003, we identified all reported cases of NF in children age 0 to 16 years from the Canadian Paediatric Surveillance Program (CPSP), an active surveillance collaborative program between the Canadian Paediatric Society and Public Health Agency of Canada. The CPSP system has been used to

CPSP	Canadian Pediatric Surveillance Program	NF	Necrotizing fasciitis
GAS	Group A streptococcus	NSAID	Nonsteroidal anti-inflammatory drug
IVIG	Intravenous immunoglobulin		

From the Department of Pediatrics, Ohio State University, Columbus, OH (I.E.); Department of Pediatrics and Human Development, Michigan State University, East Lansing, MI (I.E., H.D.D.); and Department of Pediatrics, University of Calgary, Calgary, Alberta, Canada (H.D.D.).

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Reprint requests: H. Dele Davies, MD, Pediatrics and Human Development, Michigan State University, College of Human Medicine, B240 Life Sciences Building, East Lansing, MI 48824. E-mail: daviesde@msu.edu.

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successfully monitor and ascertain rare conditions (see http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/04pdf/30s2_e.pdf). Approximately 2300 of the estimated 2500 pediatricians and pediatric subspecialists in Canada participate in this monthly surveillance system on a voluntary basis. Because of the severity of NF in Canada, management always occurs at a tertiary health care center, with care coordinated by a pediatrician. On identification of a case, an initial "check-off" form is used, followed by a detailed reporting form. The detailed reporting form serves to confirm the accuracy of diagnosis of NF before it is considered a case. The information on the form includes demographic data, presenting signs and symptoms, risk factors, primary site of infection, management, outcome, and microbiological test results. The average monthly response rate is 82%, with a >95% completion rate for detailed case reporting.

The present study was approved by the University of Calgary's Conjoint Medical Ethics Committee.

Case Definition

NF was defined as cases with positive culture from either blood or connective or fascial tissue plus histopathology results demonstrating necrosis of superficial fascia, polymorphonuclear infiltrate, and edema of the reticular dermis, subcutaneous fat, and superficial fascia, or in the absence of histology, gross fascial edema and necrosis detected at surgery or frank cutaneous necrosis seen on physical examination.[1]

Microbiology

A case was defined as GAS-related when group A streptococcus was isolated or as non–GAS-related when the isolates included other organisms, such as anaerobes, one or more facultative anaerobes such as streptococci (non–GAS), and/or *Enterobacteriaceae*.

Other Definitions

A risk factor was considered present if the case had any of the following conditions: contact with persons with confirmed GAS pharyngitis or invasive GAS disease, streptococcal pharyngitis, recent surgery, history of trauma, chronic illness, varicella within the past month, in out-of-home child-care attendance, hospitalization before onset of illness, or use of a NSAID within a week of hospitalization.[5] When onset of NF occurred more than 48 hours after a hospital admission, the case was classified as nosocomial. A history of underlying chronic illness was ascertained. A case was classified as having a complication if any of the following developed: adult respiratory distress syndrome, amputation, need for multiple surgical procedures, need for skin graft, or death.[5] Coagulopathy was defined as a platelet level at or below normal for age or the presence of disseminated intravascular coagulation. The criteria for hepatic and renal impairment were a 2-fold or greater elevation in serum alanine aminotransferase, aspartate aminotransferase, or total bilirubin and creatinine level.

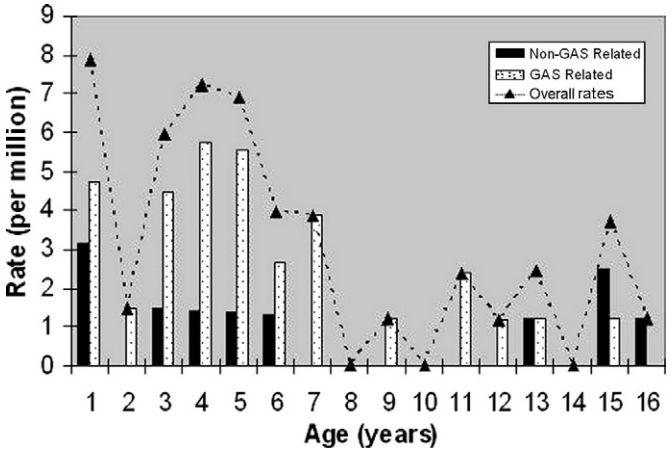

Figure 1. Incidence rates per million population by type of NF, 2001 to 2003. ▬ Non-GAS Related, ⬚ GAS Related, ···▲··· Overall rates.

Statistical Methods

The incidence of NF was determined using age-adjusted census figures for the Canadian population during the surveillance period as obtained from Statistics Canada (http://www.12.statcan.ca/english/census01/home/index.cfm). To compare incidence among groups, a normal approximation for the comparison of Poisson counts was used.[18] Statistical significances for bivariate categorical data (eg, differences between patient demographics, risk factors, and presenting signs and symptoms) were assessed using the χ^2 test or Fisher's exact test. Group means were compared using the Student t test or Wilcoxon's rank-sum test. Differences between groups were considered statistically significant at $P \leq .05$.

RESULTS

Between November 1, 2001 and October 31, 2003, 36 cases of NF were identified in children under age 16 years; 10 of these cases met the case definition for non–GAS-related NF, and 26 cases did so for GAS-related NF. Cases were reported from 7 of the 13 Canadian provinces and territories (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, and the Northwest Territories), which account for 92% of the population of Canada. The remaining provinces did not report any cases. The mean age of cases was 5.9 ± 5 years, with males constituting 49% of cases. The total annual incidence was 2.93 cases per million population under age 16 years (0.81 per million for non–GAS-related vs 2.12 per million for GAS-related; $P < .01$). The incidence was greatest during the first 5 years of life, with an overall annual incidence of 5.9 per million in this age group versus 1.8 per million in children age 5 years and older ($P = .0002$) (Figure 1). Males under age 1 year had the highest overall rates of disease (12 cases per million, vs 3.2 per million for females under age 1 year; $P < .0001$) (Figure II; available at www.jpeds.com).

Risk Factors

Twenty-nine children (81%) had at least 1 identified risk factor for NF. Seventeen cases (46%) cases occurred

within 1 month of a varicella infection. Seven cases (19%) had at least 1 underlying chronic condition, including Down syndrome; congenital neutropenia; Klippel-Trenaunay-Weber syndrome, with lower leg hemangioma, bronchopulmonary dysplasia, and recurrent bronchitis; cerebral palsy, with hydrocephalus and ventriculoperitoneal shunting; and schizophrenia, with mild developmental delay. Compared with GAS-related cases, there was a trend of non–GAS-related NF cases being nosocomial (2/10 [20%] vs 0/24 [0%]; $P = .08$), being associated with recent surgery (3/10 [30%] vs 1/26 [4.0%]; $P = .05$); and having a recent history of trauma (3/10 [30%] vs 2/23 [8.0%]; $P = .12$). A documented history of varicella in the preceding month was more common in GAS-related cases (15/25 [60%] vs 2/10 [20%]; $P = .05$), as was a trend for contact with a person with pharyngitis (9/25 [36%] vs 0/10 [0%]; $P = .07$). GAS-related cases were more likely to report the use of a NSAID within a week before the onset of disease (10/17 [58.8%] vs 0/6 [0%]; $P = .01$).

Among the 5 patients under 1 year old, only 1 had a history of a chronic condition, although 4 (80%) had a predisposing risk factor (Table I). The only infant death occurred in a 3-week-old male who had an abdominal infection originating the umbilical stump.

Clinical Presentation

The median time from onset of illness to coming to medical attention (excluding the 2 nosocomial cases) was 1 day. The most common presenting symptoms were localized pain (34/35; 97.1%), chills (12/34; 35.3%), and vomiting (9/33; 27.2%). Sore throat and respiratory symptoms (eg, cough, shortness of breath, sore throat) were more common in GAS-related NF (Table II).

Rash was the predominant finding on physical examination. Of the 26 cases that presented with a rash, generalized rash was seen only in GAS-related cases ($P < .05$). Desquamation during the hospital stay occurred in only 1 case (2.8%), a GAS-related NF case. Toxin-mediated physical examination findings (eg, generalized rash, conjunctivitis, strawberry tongue) occurred more frequently in GAS-related NF (14/26 vs 0/10; $P = .006$).

The median temperature at presentation was 38.6°C (range, 36.1 to 40.3°C). Seven of the 36 patients (19%) were hypotensive, requiring treatment with pressor agents. The majority (5/7; 71.4%) of the hypotensive patients were over 5 years old. Hypotension was more frequent in non–GAS-related cases (4/10; 40%) than in GAS-related cases (3/26; 11.5%), but the difference was not statistically significant ($P = .07$). Sixteen cases (44%) involved the lower extremities or groin area; 7 (19%) involved the upper extremities; 8 (22%) involved the head, neck, and chest; and 3 (8%) involved the abdomen. One infant had lesions in multiple sites. Non–GAS-related NF occurred more commonly on the lower extremities, groin, and abdomen (Figure 3); only 1 child had a lesion on the head and neck area.

Table I. Risk factors, presentation, and outcome of necrotizing NF in patients under 1 year old

Patient	Age	Sex	NF type	Chronic condition	Risk factor	Site	Source of organism	Complication	Length of stay (days)	Outcome
1	3 weeks	M	Non–GAS*	No	Trauma	Abdomen (umbilical stump)	Tissue Aspirate	Coagulopathy Rash Renal impairment	3	Death
2	8 months	M	GAS	No	Surgery NSAIDs	Abdomen Groin	Blood Tissue Aspirate	Rash	10	Survival
3	4.5 months	F	Non–GAS†	Yes‡	Prematurity Surgery BPD IVH	Cheek and neck§	Blood	Coagulopathy Amputation¶	53	Survival
4	5 weeks	M	GAS	No	None	—	Tissue	Rash	36	Survival
5	10.5 months	M	GAS	No	Varicella	Shoulder	Tissue Aspirate	Rash	10	Survival

BPD, Bronchopulmonary dysplasia; *IVH*, intraventricular hemorrhage.
*Staphylococcus aureus.
†Group B streptococcus.
‡Down syndrome.
§Suspected spider bite.
¶Amputation of part of the left ear.

Table II. Clinical presentation of non–GAS-related and GAS-related NF

Characteristic	Non–GAS-related NF		GAS-related NF	
	n	%	n	%
Symptoms				
Abdominal pain	3/10	30	2/25	8.0
Chills	4/9	44	8/25	32
Confusion	1/10	10	1/25	4.0
Cough	0/9	0	4/25	16
Diarrhea	0/10	0	3/25	12
Diffuse myalgia	0/10	0	2/25	8.0
Headache	1/10	10	2/25	8.0
Local pain	10/10	100	24/25	96
Shortness of breath	1/9	11	0/24	0
Sore throat	0/9	0	6/25	24
Syncope	1/10	10	1/24	4.2
Vomiting	1/9	11	8/25	33
Physical examination and laboratory findings				
Rash	6/10	60	21/26	73.0
Generalized*	0/6	0	13/20	65.0
Local*	6/6	100	7/20	35
Desquamation	0/10	0	1/25	4.0
Mucous membrane hyperemia	1/10	10	6/24	25
Conjunct	0/4	0	4/12	33
Strawberry tongue	0/4	0	2/13	15
Pharyngeal exudates	0/4	0	4/14	28
Elevated liver enzymes	1/10	10	2/26	7.7
Renal impairment	2/10	20	2/26	7.7
Coagulopathy	5/10	50	5/26	19
Complications	7/10	70	21/26	81
Adult respiratory distress syndrome	1/10	10	2/26	7.7
Amputation†	1/10	10	0/26	0
Fatal outcome	2/10	20	0/26	0
Skin graft	4/10	30	6/26	23.1
Multiple surgical procedures	7/10	70	21/26	81

*$P < .05$.

†Amputation of left ear in a 4.5-month-old male.

Microbiology

All of the patients had a positive blood, tissue, or aspirate culture. The highest yields were from tissue cultures—50% for non–GAS-related cases and 85% for GAS-related cases (Table III; available at www.jpeds.com). However, there was a significantly greater likelihood of isolation of the organism from skin or tissue culture in GAS-related cases (Table III). Isolated organisms in non–GAS-related cases included group B streptococcus, *Staphylococcus epidermis*, *S. aureus*, *E. coli*, *Bacteriodes fragilis*, *K. pneumoniae*, and *Clostridium septicum*.

Management and Outcome

Penicillin and clindamycin were the most commonly administered antibiotics. All 10 non–GAS-related patients received penicillin or another beta-lactam antibiotic (with 2 patients receiving a first-generation cephalosporin and 4 receiving a third-generation cephalosporin); 8 also received clindamycin. Other antibiotics used for non–GAS-related cases included vancomycin, aminoglycosides, and metronidazole. All GAS-related patients received clindamycin in combination with either penicillin (22/25 cases; 1 case undocumented) or another beta-lactam antibiotic (3/26 cases). Nineteen patients (14/26 [54%] GAS-related and 5/10 [50%] non–GAS-related) received unspecified blood products.

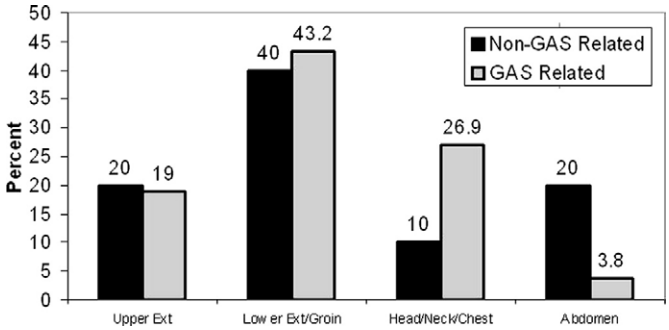

Figure 3. Location of lesions in the non–GAS-related and GAS-related NF cases. ■ Non-GAS Related, □ GAS Related.

NF-related complications were observed in 28 cases (78.0%). The frequency of complications was similar in both types of NF (Table II) except for fatal outcome, which occurred only in non–GAS-related cases. All of the patients underwent a surgical procedure; 78% (28/36) had a second surgery, and 50% (18/36) had a third surgery. Skin graft rates were similar in GAS-related and non–GAS-related cases.

The median length of hospital stay was 12 days (range, 5 to 81 days). The length of stay was longer for non–GAS-related cases (median, 33 days; range, 12 to 81 days) compared with GAS-related cases (median, 12 days; range, 5 to 36 days; $P = .004$. The proportion of cases admitted to the intensive care unit was similar in both types of NF (60% vs 62%; $P = 1.0$). Non–GAS-related cases had a greater tendency to receive pressor agents (4/10 vs 3/26; $P = .17$) and to require mechanical ventilation (5/10 vs 7/26; $P = .24$). Two deaths (both non–GAS cases) occurred during the surveillance period, for an overall case fatality rate of 5.4%. One death was the youngest patient, and the other was a 5-year-old boy with congenital neutropenia who presented with a rapidly spreading violaceous lesion on the right buttock. *K. pneumoniae* and *C. septicum* were isolated from a biopsy specimen of the lesion.

DISCUSSION

In this population-based active surveillance study, we found an annual incidence of NF in children of 2.93 cases per million population per year, with 0.81 per million for non–GAS-related cases and 2.12 per million for GAS-related cases. Although there are no comparable baseline rates for non–GAS-related NF, our GAS-related NF rate is somewhat higher than the annual total population incidence rate of 1.3 cases per million in the population of Ontario between 1992

and 1996,[7] but similar to the 2.5 cases per million reported in a study of invasive GAS in Alberta between 2000 and 2002.[8] For both of these studies, the focus was not on NF (each had fewer than 10 pediatric NF cases), but on invasive GAS infections. As reported previously for other invasive GAS diseases, males and younger children had the highest incidence.[7,10] Although morbidity, defined as the presence of complications, was similar for both non–GAS-related and GAS-related cases, GAS-related NF was associated with a lower case fatality rate (0% vs 20%; $P = .07$).

NF typically occurs in the presence of disruptions to the skin, respiratory tract, or perineal region or genital tract.[2,4,13,19] Our study confirmed that in children, more than 50% of non–GAS-related NF occurs in individuals with an underlying medical condition, such as diabetes mellitus, trauma, or recent surgery. In contrast, few children with GAS-related NF (11%) have an underlying medical condition (except for recent varicella). The prevalence of an underlying condition in GAS-related NF is similar to the estimate of 16% previously noted for pediatric invasive GAS infections in general.[7]

Non–GAS-related NF occurs most frequently in infants under age 1 year.[2,4,13,14] All of the infants in our study had either an existing risk factor (eg, prematurity) or an underlying chronic condition that likely increased their susceptibility to the infection. In the under-1-year group, non–GAS-related NF involving the abdomen occurs most commonly in association with omphalitis.[2,4,13,14]

The majority of GAS-related cases (~60%) had a preceding varicella infection, a finding consistent with other studies showing an association with invasive GAS disease.[5,7,17,20-26] This information will be useful for monitoring the impact of Canadian varicella vaccine programs on NF. Patel et al[27] found that the incidence of varicella-associated invasive GAS hospitalizations in Chicago decreased from 27% in the prevaricella vaccine era (1993 to 1995) to as low as 2% during a period of widespread vaccine use between 1999 and 2001. Varicella infection is postulated to lead to a breakdown in the protective barrier in the skin, oral mucosa, or respiratory tract, thereby increasing the susceptibility to infection from GAS.[7] Furthermore, a predominance of T_{H1}-type response in association with a varicella infection may lead to a relative decrease in humoral immune response and predispose to bacterial infections.[7]

Although varicella vaccine was licensed in Canada in 1998, at the onset of our study in January 2003, only 3 of 10 provinces (Alberta, Nova Scotia, and Prince Edward Island,) and 2 of the 3 territories (Northwest Territories and Nunavut) had fully implemented a publicly funded immunization program.[28] Since 2004, most Canadian provinces and territories have initiated programs for catch-up immunization of high-risk patients and universal varicella vaccination at age 12 months. Our study will enable further evaluation of the impact of these new vaccination programs.

In this study, at least 50% the patients with GAS-associated NF had taken a NSAID within 1 week before presentation. NSAIDS impair granulocyte functions, including chemotaxis, phagocytosis, and bactericidal activity.[29] Some investigators have hypothesized that NSAIDS increase the risk of GAS-related NF, especially in children with varicella.[17,22,29-31] Although 1 case-control study[22] found an association between ibuprofen use and GAS-related NF, 5 subsequent cohort studies have not confirmed such an association.[1,7,21,32,33] However, only 1 of these studies[32] was specifically designed to test the hypothesis that NSAIDs increase the risk of severe invasive GAS disease and NF; the association with NSAIDs in that study was thought to be due to confounding by indication. It is unclear whether NSAIDs contribute to GAS-related NF or lead to a spurious association due to their use for pain and fever control in the early phases of the illness. Nonetheless, clinicians managing patients at risk for or with suspected NF or invasive GAS disease should prescribe NSAIDs cautiously, especially in children with varicella.

In the present study, all patients were treated with penicillin or a beta-lactam antibiotic, and 83% were treated with clindamycin. GAS remains universally sensitive to penicillin. However, concerns about the clinical failure rates with penicillin despite microbiologic sensitivity in other GAS infections, findings of improved outcomes in animal models, and clinical studies have led to the frequent addition of clindamycin to antibiotic regimens.[19,34-37] We did not ascertain whether intravenous immunoglobulin (IGIV) was used in our study population. The use of IGIV as an adjunct to treatment for NF merits a comment.[34,36-39] Results of it use have been mixed. The only multicenter controlled trial of IGIV as an adjunctive therapy for streptococcal toxic shock syndrome was terminated after about 20% of the planned enrollment had occurred, due to slow enrollment.[39] Yet in another study, 7 adult patients with NF in Ontario were treated with high-dose IGIV in conjunction with antibiotics and needed only minimally invasive procedures or no surgery.[38] In 1 patient who underwent serial biopsies, investigators detected a quantitative decline in GAS, superantigen, and cytokine levels 66 hours after a high dose of IGIV.[38]

A potential limitation of our study is the reliance on reporting from physicians in the CPSP, which may lead to an underestimation of the real incidence. However, the provision of active monthly surveillance reminders to all participating physicians reduces the likelihood of missed cases and helps tracks participation rates. The participation rate in this CPSP study was >80%, and the 7 provinces from which cases were reported represent 92% of the total population of Canada. Using a 2-tiered data collection system improved the completeness of data collection. In addition, the incidence rates that we found were similar to rates reported in studies using other methodologies.

Previous reports on NF in the pediatric population have been case reports or series or have focused on NF as a component of invasive GAS disease,[1,5-7,12,27] with only limited characterization of the risk factors, clinical presentation, and outcomes of NF. One strength of surveillance tools such

as the CPSP is that they promote better understanding of the epidemiology of rare diseases such as NF. Our findings serve as baseline population data for rates, clinical presentation, and outcomes as varicella immunization uptake expands in Canada.

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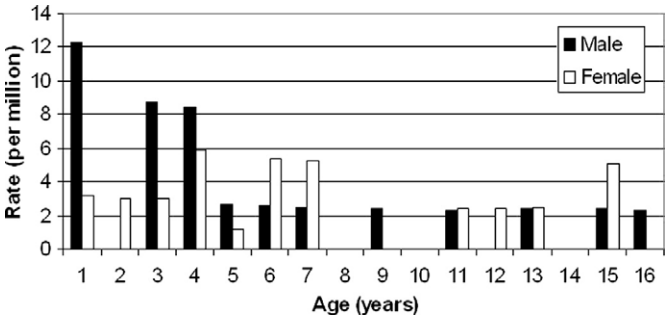

Figure 2. NF incidence rate per million population by sex. ■ Male, □ Female.

Table III. Source of pathogens in NF classified by type

Site	Non–GAS-related		GAS-related	
	n	%	n	%
Sterile site				
Blood culture	1/10	10	5/26	19
Tissue biopsy*	4/8	50	21/25	84
Aspirate culture	2/8	25	11/24	46
Nonsterile site				
Throat culture	0/8	0	8/23	35
Skin culture*	1/8	12	5/21	24
Wound culture	4/8	50	8/21	38

*$P < .05$.