

# **Epidemiology & Infection Bulletin**

- 105 Flesh-Eating Bacteria:  
Current Situation of  
Group A Streptococcal  
Infectious Gangrene in  
Taiwan
- 116 Cases of Notifiable and  
Reportable Diseases,  
Taiwan-Fukien Area

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## **Flesh-Eating Bacteria: Current Status of Group A Streptococcal Infectious Gangrene in Taiwan**

### **Abstract**

Twenty-seven cases of group A streptococcal infectious gangrene were collected from Taiwan medical centers between January 1991 and June 1994. These included 4 cases of invasive cellulitis, 14 cases of necrotizing fasciitis and 9 cases of streptococcal toxic shock-like syndrome (STSS) as a complication of necrotizing fasciitis. The leading underlying disease for all 27 cases was diabetes (8/27, 29.6%); the most common predisposing factor was trauma (13/27, 48.1%). Clinical symptoms included reddening, swelling and pain of local soft tissue, fever and bullae. Invasion of the lower limbs was most common (17/27, 62.9%). The relevant clinical factors from the three groups showed no significant differences. Treatment was primarily by the use of antibiotics and surgical debridement/drainage. Prognosis in general was good. However, there were 6 deaths and all belong to the group with STSS. Therefore, risk factors of STSS such as older age, hypotension, renal impairment, diarrhea, group A streptococcal bacteremia should be identified as early as possible for active treatment. The specific mechanism of group A streptococcal toxic shock-like syndrome in Taiwan requires further investigation and research.

### **Introduction**

In May 1994, one newspaper in the United Kingdom headlined the shocking news of a "flesh-eating bacteria"<sup>(1)</sup>. The bacteria were said to eat into human skin and to cause damage and gangrene in the flesh. Photos of patients with injured faces suddenly became sensational international news. It was as though a new paranta-like bacteria had evolved in human infections. This piece of information certainly created another ripple and panic in the 1990 world, already much disturbed by growing awareness of AIDS. It was, however, later proved that the "flesh-eating bacteria" incident was merely an attention-getting medical news story, sourceable to the media. The "flesh-eating bacteria" were none other than the old, traditional bacteria historically present in humans -- the group A *Streptococcus*. Even in the

pre-microscope era when the theory of bacteria as a cause of disease had not yet been proposed, these bacteria had already caused pyogenic infections in war injuries and surgical wounds<sup>(2)</sup>. In 1846, Semmelweiss made the remarkable discovery that the deadly substance transmitted between a cadaver undergoing autopsy and a woman at delivery was proved later exactly, group A *Streptococcus*<sup>(3)</sup>. These bacteria often induce community infections such as cellulitis, suppurative tonsillitis and scarlet fever. The sequelae from such diseases as rheumatic heart disease and post-streptococcal nephritis are major challenges for those in the medical field. Group A *Streptococcus* can produce many toxins which invade skin and soft tissue, and occasionally demonstrate necrosis and ulcers of the skin or the fasciae, and even gangrenous disorders in the flesh. That is how they have come to be misunderstood and misdescribed as "flesh-eating", per the scare story noted above. In fact, as early as 1924, Meleney for the first time reported cases of necrotizing fasciitis -- *Streptococcus* gangrene caused by hemolytic *Streptococcus*<sup>(4)</sup>. However, since mid-1980, group A *Streptococcus* has appeared in a new form called the streptococcal toxic shock-like syndrome (STSS)<sup>(5,6)</sup>, which also produces necrosis of the fasciae. STSS should be reviewed as well. The present work was planned and supported by the Bureau of Communicable Disease Control, Department of Health (DOH). The survey focused on recent Taiwan Area cases of infectious gangrene of the soft tissue caused by group A *Streptococcus*, after the cases were collected for analysis.

## Materials and Methods

A retrospective approach for analysis of cases was used in this survey. The Communicable Disease Bureau asked, in a letter to all medical centers, for reports of all cases of group A streptococcal infectious gangrene seen in the last three years. Group A streptococcal infectious gangrene was defined as an infectious gangrene exhibiting rapidly progressive infection of the soft tissue with a wide range of complications of necrosis of either the superficial or deep tissues (such as fasciae, muscle, *et cetera*)<sup>(7)</sup>. The present survey analyzed cases with the following symptoms:

- 1) traditional cellulitis with complications of the necrotizing defect of local skin; that is, invasive cellulitis.

- 2) necrotizing fasciitis, defined as an acute infection of the soft tissue which has invaded either the superficial or the deep fasciae. The clinical judgment and operative findings of surgeons were accepted in reviewing these data. Another criterion was that group A *Streptococcus* should also have been isolated either from the infected site or from the patient's blood culture. Cases meeting the criteria outlined above were accepted for analysis.

Cases meeting the criteria for STSS were analyzed separately to compare necrotizing fasciitis with and without STSS, while being alert to any similarity or difference in the factors between the two. The US Centers for Disease Control (CDC) in 1993 had defined STSS as:

**I. Isolation of group A *Streptococci* (*Streptococcus pyogenes*)**

From a normally sterile site (blood, cerebrospinal, pleural or peritoneal fluid, tissue biopsy, surgical wound, etc.)

**II. Clinical signs of severity**

A. Hypotension: systolic blood pressure of  $\leq 90$  mmHg in adults or  $< 5$ th percentile for age in children

B. At least two of the following signs:

1. Renal impairment: creatinine  $\geq 2$  mg/dL ( $\geq 177$   $\mu$ mol/L) for adults or greater than or equal to twice the upper limit of normal for age. In patients with preexisting renal disease, a  $\geq$  twofold elevation over the baseline level.
2. Coagulopathy: platelets  $\leq 100,000/\text{mm}^3$  ( $\leq 100 \times 10^9$  /L) or disseminated intravascular coagulation defined by prolonged clotting times, low fibrinogen level and the presence of fibrin degradation products.
3. Liver involvement: alanine aminotransferase, aspartate aminotransferase or total bilirubin levels greater than or equal to twice the upper limit of normal for age. In patients with preexisting liver disease, a  $\geq$  twofold elevation over the baseline level.
4. Adult respiratory distress syndrome defined by acute onset of diffuse pulmonary infiltrates and hypoxemia in the absence of cardiac failure, or evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia.
5. A generalized erythematous macular rash that may desquamate.
6. Soft-tissue necrosis, including necrotizing fasciitis or myositis, or gangrene.

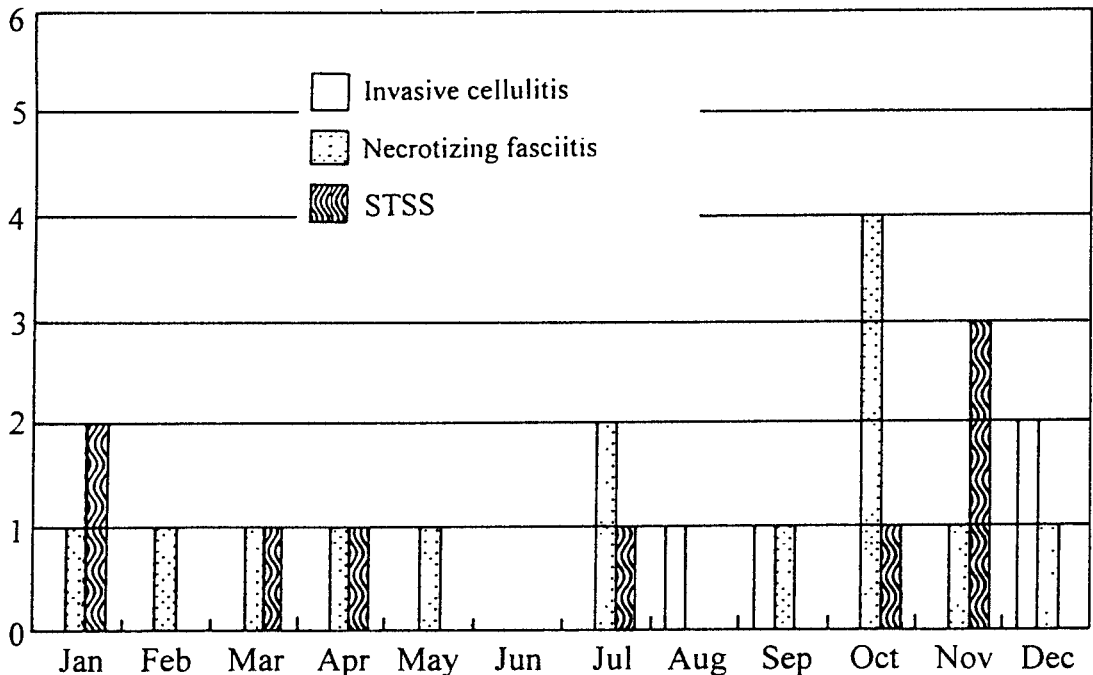
Cases thus collected were statistically analyzed with chi-square, ANOVA and t-test by age, sex, underlying diseases, predisposing factors, sites of infection, clinical symptoms and prognosis. A significant difference was set at  $p < 0.05$ .

**Results**

Between January 1991 and June 1994, 30 cases were collected from medical and provisional medical centers such as the Taipei, Taichung and Kaohsiung Veterans General Hospitals; Taipei and Kaohsiung Chang Gung Memorial Hospitals; Taipei Mackay Memorial Hospital; Cathay General Hospital; National Cheng-Kung University Hospital and the Kaohsiung Medical College Hospital. From these 30 sources, 27 cases met the criteria for group A *Streptococcus*-infected gangrene. By region, 17 cases came from the southern, 9 from the northern and 1 from the central part of Taiwan. Of those 27 cases, 4 were cases of invasive cellulitis (the first group); 14 were cases of necrotizing fasciitis (the second group); and 9 were cases of STSS (the third group). The distribution of cases by month is shown in Figure 1. As can be noted, more than half (16/27) were found in autumn and winter -- that is, in October through February. The male/female sex ratios were 3:1 in the first group; 10:4 in the second group;

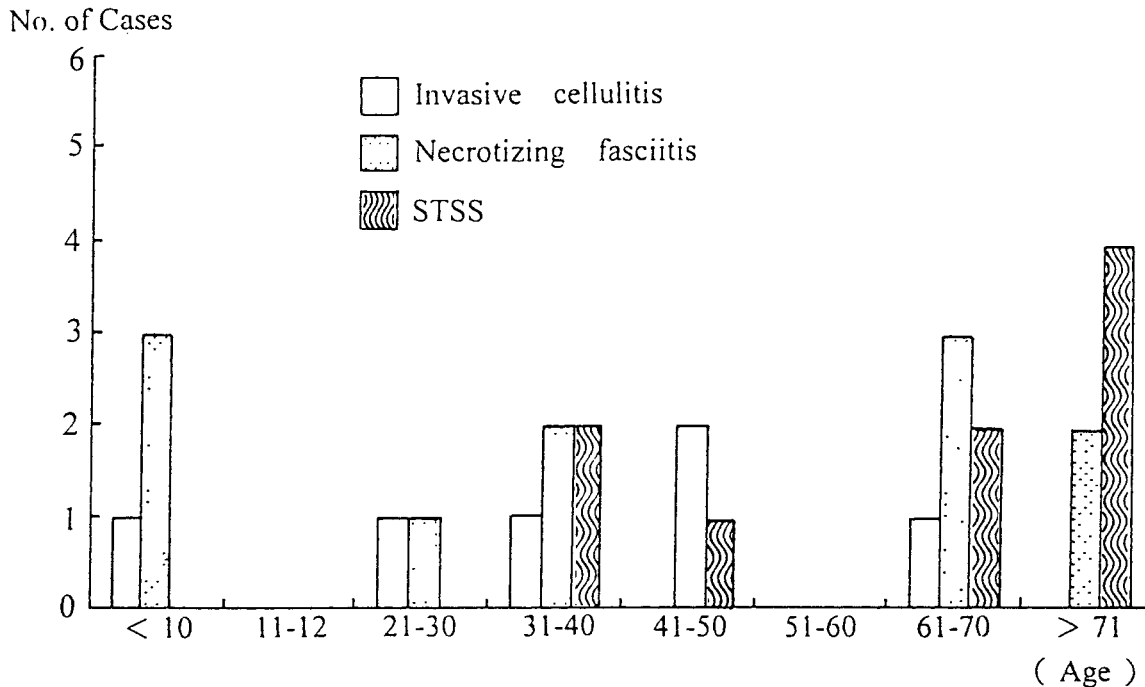
**Figure 1. Cumulative monthly Cases of Group A Streptococcal Infectious Gangrene by Month (1991 through 1994)**

No. of Cases



and 7:2 in the third group; thus, there were comparatively more men than women affected across the groups. The age distribution of cases is shown in Figure 2. The average age for each group was  $34.0 \pm 27.7$ ;  $43.6 \pm 26.1$  and  $60.9 \pm 18.7$  years, respectively (average age  $\pm$  standard error). Though no significant difference was noted in the average ages (ANOVA test  $p=0.131$ ), that of the third group seemed higher. Distribution of underlying diseases and predisposing factors of diseases are shown in Table 1. Diabetes was the most common of the underlying diseases; trauma was the most common predisposing factors. Relevant factors among the three groups did not show significant differences. Clinical symptoms are shown in Table 2. Typical inflammatory reactions such as local reddening, swelling, pain and fever were common symptoms. Bullae at the inflamed sites, not commonly seen in ordinary cellulitis, ranked number 5, with 44.4%. Of clinical symptoms, diarrhea was seen only in cases of STSS, a finding of statistical significance ( $p=0.034$ ). The infected sites of all four cases of invasive cellulitis gave purulent or serosanguineous discharges, as one of the criteria for the case definition. Of the three groups, the STSS patients often associated with group A streptococcal bacteremia (5/8, 62.5%). The sites of invasion are shown in Table 3. Limbs, particularly the lower limbs, were most commonly invaded (17/27, 62.9%). Of the organs, in addition to the soft tissue, STSS caused more renal impairment (7/9, 77.8%), in non-STSS group, only one case showed a decline

**Figure 2. Distribution of Cases of Group A Streptococcal Infectious Gangrene by Age (1991 through 1994)**



in blood pressure. All the 27 cases were treated with antibiotics and surgical debridements/drainages. The overall mortality rate of 22.2% (6/27) applied only among STSS ( $p < 0.05$ ) patients; that is, the mortality rate for STSS patients was 66.7%.

## Discussion

Group A *Streptococcus* was recognised, even in the 19th Century, as a classical human pathogens. It attacked primarily the soft tissue or throats of humans, and some times causing rheumatic fever or nephritis. Many people have studied its toxicity<sup>(9)</sup>. Toxins of the bacterium include hyaluronic acid of the cell membrane which can resist the phagocytosis of white blood cells; lipoteichoic acid and F protein of the cell wall which help bacteria to colonize on epithelial cells of humans; and T protein and M protein also in the cell walls. T protein is more related to bacterial typing; M protein is closely related to the toxicity of group A *Streptococcus* and can initiate diseases<sup>(10,11)</sup>. Group A *Streptococcus* can intensify its virulence through exotoxins such as streptolysin O&S which can destroy red blood cells, and even white blood cells and platelets.

**Table 1. Underlying Diseases and Predisposing Factors of Cases of Group A Streptococcal Infectious Gangrene**

Item	Invasive cellulitis N=4	Necrotizing fasciitis N=14	STSS N=9
Underlying diseases:			
Diabetes	1	4	3
Steroid use	1	2	3
Oral herbal pills	0	2	2
Alcoholism	1	1	1
Malignant neoplasms	1	0	2
Nephrotic syndrome	1	1	0
Gout	0	1	1
Predisposing factors:			
Trauma	2	8	3
Direct herb application	1	1	2
Chickenpox	0	3	0
Insect bites	1	0	1
Bed sore	0	1	0
Operation	1	0	0
Dental caries	0	1	0
Spontaneous	0	0	1

Other enzymes such as DNase, hyaluronase and streptokinase can destroy the structure of connective tissues, and enhance the invasion and spreading of group A *Streptococcus* in the soft tissue.

Group A *Streptococcus* is not a normal flora of the skin. However, under optimal circumstances it can, through the help of F protein, colonize on human skin. When there is leakage through the skin as a result of a minor wound, scratch or insect bite<sup>(12)</sup>, the bacteria will invade the epidermis and beyond through the secretion of toxins, causing cellulitis. Clinically, signs of local inflammation such as swelling, pain and redness are common, and on occasional bullae can be noted, but an obvious skin defect is rare. Underlying disease are mostly tinea pedis, lymphedema, of the lower limbs or cardiovascular bypass surgery. For only a few patients -- (the CDC estimate in 1992 was 5 to 10%<sup>(13)</sup>) -- group A *Streptococcus* than invades the deep soft tissue to induce serious necrotizing fasciitis or the so-called "flesh-eating" appearance.

Table 2. Clinical Symptoms of Group A Streptococcal Infectious Gangrene

Item	Invasive cellulitis N=4	Necrotizing fasciitis N=14	STSS N=9
Swelling of wounded area	3	11	6
Reddening of wounded area	3	11	5
Pain of wounded area	4	9	6
Fever	4	9	5
Bullae	1	6	5
Discharge at wounded area <sup>+</sup>	4	3	3
Skin ulcer	1	4	4
Gangrene of soft tissue	1	3	1
Chilliness	1	1	2
Nausea/vomiting	0	2	2
Diarrhea*	0	0	3
Change of consciousness	0	0	1
Bacteremia	0	2	5
Hypotension**	0	1	9

\* Chi-square test, Global,  $p=0.034$

\*\* Chi-square test, Global,  $p < 0.001$ , difference in the definitions of cases

+ Chi-square test, Global,  $p=0.033$ , difference in the definitions of cases

The present survey collected 27 cases within a period of three and a half years. There is only one medical center in central part of Taiwan, Taichung Veterans General Hospital, making it appear that more cases come from the southern and the northern parts of the Island, particularly the former, with 17 cases. Whether warm weather and the life style in the more tropical South increased the exposure of skin and also gave more opportunity for injuries<sup>(14)</sup> needs further study. By severity, only 4 cases were of invasive cellulitis with complications of skin ulcer/gangrene; the other 23 were cases of necrotizing fasciitis. Literature shows that necrotizing fasciitis was first discovered by Meleney in 1924 in China; it was named "streptococcal gangrene", and the agent of infection should have been group A *Streptococcus*. However, according to modern medicine, a typical necrotizing fasciitis should be a mixed

**Table 3. Sites of Invasion and Sequelae of Group A Streptococcal-Infectious Gangrene**

Item	Invasive cellulitis N=4	Necrotizing fasciitis N=14	STSS N=9
Site of infection			
Necrotizing fasciitis	0	14	9
Lower limbs	3	10	4
Upper limbs	1	1	3
Head and neck	0	1	1
Psoas muscle	0	1	1
Trunk	0	1	0
Sites of invasion			
Necrotizing fasciitis	0	14	9
Kidney	0	1	7
Liver	1	0	3
Gastro intestinal tract	0	0	3
Hematology	0	0	2
Lung	0	0	1
Died*	0	0	6

\* Chi-square test, Global,  $p < 0.05$

infection caused by pathogenic agents including at least one anaerobic bacterium and another gram-negative bacillus<sup>(15)</sup>. Ou's study shows that, of the 58 cases of necrotizing fasciitis seen in the last 6 years in the Taipei Veterans General Hospital, 20% were typical infections by the above definition, and only 2 cases were actually caused by group A *Streptococcus*. Similar reports are found elsewhere<sup>(16,17)</sup>. It seems, therefore, that necrotizing fasciitis caused by group A *Streptococcus* is rare, and that its pathogenesis is different from that of the mixed infection of anaerobic bacteria. This may be related to the specific toxins produced by group A *Streptococcus*.

More men than women were affected, possibly because men are more likely to be injured through more frequent exposure to the outside world. The underlying illness were diabetes (8 cases), use of steroids (6 cases), use of black pills a so-called scientific herbs prepared in a form of black-colored pills (4 cases), and alcoholism, malignant neoplasms, chickenpox and nephrotic syndromes, covering in varying



degrees all deficiencies of immune functions such as skin barriers, phagocytosis and cell mediated immunity. Predisposing factors included trauma (nine cases) by cuts, scratches and thorn pricks; four cases had used herbal drugs by placing them directly upon wounds; other patients were victims of chickenpox or insect bites which had injured the skin and allowed a considerable amount of bacteria to penetrate, causing infection. These underlying disease, predisposing factors differ from those of cellulitis and are similar to those reported elsewhere<sup>(18,19)</sup>, except for the following: firstly, it is a well-recognised indigenous custom to use black pills, which frequently contain steroids and may reduce cell mediated immunity secondly, the application of herbal drugs locally, and these are often unsterilised and apply more bacteria directly to a wound, resulting in necrotic infection. "Spontaneous infection" has been mentioned frequently by foreign literature in recent years; that is, patients are often healthy young persons without either underlying or predisposing factors involved. In the present survey, in only one case was no pathogenic factor found.

The clinical symptoms of the 27 cases were primarily local reddening, swelling, pain and fever, all typical of infection of the soft tissue; 44.4% had developed bullae. This symptom should help early differential diagnosis from classical infections of the soft tissue. Infectious necrosis, or the "flesh-eating appearance", such as ulcer, gangrene, local purulent or serosanguineous discharges, developed in only 19-37% of the patients at the initial stage. Diarrhea and change of consciousness were systemic manifestations and were seen only in STSS patients in the present survey. Although they did not meet the CDC criteria for case definition, they should not be ignored.

Nine cases (33.3%) had developed STSS. By definition, they showed clinically hypotension, necrotizing fasciitis and the invasion of at least one organ. In terms of the invasion of organs, renal impairments were the most common with seven cases. This finding is similar to that of other reports<sup>(19,20)</sup>. However, of the nine cases, none had developed skin rash or desquamation a finding different from that in foreign reports. With the exception of one case for whom no blood culture was done, the other five cases (62.5%) had developed bacteremia. Though the finding was not statistically significant, it was more than had been expected. According to the literature<sup>(21)</sup>, the fact that children with invasive group A streptococcal bacteremia seem to have a lower rate of STSS than adults indicates that bacteremia is not an absolutely essential factor of STSS. However, bacteremia means invasion by a large amount of bacteria. Together with other immunological defects, it can be a pathogenic factor of STSS.

Since the 1980's, the number of STSS patients in Europe and America has increased and has thus received more attention. Patients often are healthy young people without underlying diseases. Studies abroad have indicated that their pathogenic factors are related to the streptococcal pyrogenic exotoxin (SPE) produced by M1 or M3 group A *Streptococcus*<sup>(22,23)</sup>. SPE was named "erythrogenic toxin" because it could induce skin rashes in scarlet fever patients. Of the SPEs SPE A act as a super-antigen in the syndromes, elicits the human cytokines to produce a series of autoimmune response, thus bringing about clinical outcomes similar to those of septic shock<sup>(24)</sup>. However, the findings of the present survey differ from those in foreign reports: patients were older, and with underlying illness. Local studies of the SPE genes of group A *Streptococcus* (Kaohsiung Veterans' General Hospital, Taiwan Provincial Tainan Hospital) have not shown the

important role played by SPE A. Along with the fact that skin rashes or desquamation are rare among local patients, the pathogenicity of STSS in Taiwan is perhaps different from that in other countries. Speculations are that patients in Taiwan have multiple factors such as the invasion of protease of SPE B into the deep tissue, the invasion of a large amount of bacteria, old age, immune deficiency and others. Whether there are other exoproteins playing the role of super antigens and whether this factor is related to the specific M protein subgroup of group A *Streptococcus* in Taiwan needs further study.

The treatment of infectious gangrene is primarily through the use of antibiotics and surgical debridements/drainages. Group A *Streptococcus* is still sensitive to most antibiotics, and the choice of antibiotics is not a crucial factor for prognosis, though penicillin is the preferred choice. Surgical debridements/drainages should be done early and supplemented later by skin grafting. Prognosis in general are good. As 6 deaths out of the 27 cases were all cases of STSS, risk factors of STSS such as old age, hypotension, renal impairment, diarrhea, disturbed consciousness and bacteremia should be identified early and treated promptly with adequate surgical debridement/drainage and other therapeutic methods recommended in the literature<sup>(25)</sup>. Such as use of clindamycin to inhibit the production of toxins, intravenous immunoglobulin or plasmapheresis to neutralize toxins, *etc.*

This report concerns the so-called "flesh-eating bacteria" mentioned in the last three to four years, as investigated in the Taiwan Area. It provides a clinical alert when examining patients in high risk groups, and encourages physicians to offer such victims early treatment, which is effective. Further studies of pathogenesis and the toxins involved should be the task of fellow physicians.

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