Invasive Streptococcal Group A Infection and Toxic Shock Syndrome in Songklanagarind Hospital†

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Abstract

Background and Objectives : Streptococcal group A infection is reported as a medical problem in several parts of the world. The most serious complication of this infection is streptococcal toxic shock syndrome (STSS) which is associated with a very high mortality rate. The present study aimed to determine the clinical manifestations, including underlying conditions, mortality and prognostic factors, of invasive streptococcal group A infection and STSS from southern Thailand (Songklanagarind Hospital).

Method : The medical records of infected patients from January 1, 1995 to June 30, 1999 were reviewed retrospectively. Criteria for diagnosis of STSS were as follows (JAMA 1993). Prognostic factors were analyzed by logistic regression model.

Result : 176 cases of STSS and streptococcal group A infection, 89.9 per cent were community acquired infections. About 70 per cent of the infected patients had previous underlying conditions, the most common was cancer. The commonest site of infection was the skin and soft tissue (80.1%). The total mortality rate from streptococcal group A infection was 9.1 per cent. STSS was identified in 12 patients (6.8%), with a 50 per cent mortality rate. Prognostic factors for mortality in this infection were diabetic mellitus (odds ratio 9.67, $p<0.025$), history of steroid use (odds ratio 11.17, $p<0.017$), STSS (odds ratio 22.16, $p<0.005$) and received cancer chemotherapy (odds ratio 115.19, $p<0.003$). Predictive factors for STSS couldn't be identified, while age >65 years and steroid use were suggested protective factors for this condition {odds ratio 0.02, $p<0.0001$ and odd ratio 0.07, $p<0.027$ respectively}.

Key word : Invasive Streptococcal Group A Infection, STSS, Streptococcal Toxic Shock Syndrome

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Streptococcus group A or *Streptococcus pyogenes* is a gram positive cocci organism that produces various human infections such as pharyngitis, erysipelas, cellulitis[1], pneumonia, post partum infection etc. Necrotizing fasciitis is deep soft tissue infection, with rapid progressive deterioration and often death. Important post-infectious complications are acute glomerulonephritis and rheumatic heart disease, leading to morbidity from renal failure and rheumatic heart disease, respectively.

After the discovery and world wide use of antibiotics, this infection has largely been controlled. However, about ten years ago, there was an increase in the incidence and severity of streptococcal group A infection in North America, Europe and Asia[2-8]. Since 1987, streptococcal toxic shock syndrome (STSS) has been identified with fulminant streptococcal group A infection associated with shock, and multi-organ failure, including liver, kidney, hematology and the respiratory system[9-11]. This syndrome is also usually, related with a very high mortality rate.

In Thailand, there have been a few reports of streptococcal group A infection and streptococcal toxic shock syndrome[6,12-14], however, there have been no data reviews or reports from southern Thailand. The purpose of this study was to examine the incidence of invasive streptococcal group A infection and STSS, to define the spectrum of disease, clinical characteristics, associated underlying conditions, mortality rate and prognostic factors that determined the outcome of the disease, in southern Thailand.

METHOD

The authors contacted the microbiological laboratory of Songklanagarind Hospital to identify the positive culture specimens of streptococcal group A between January 1, 1995 and June 30, 1999. Medical records were reviewed retrospectively for patients who had the complete inclusion criteria. The patients were diagnosed with invasive streptococcus group A disease when they had one or more positive culture specimens from a sterile site that usually had no flora contamination. The specimens included hemoculture, cerebrospinal fluid (CSF), pleural fluid, ascites, clean catch midstream urine, synovial fluid, pus from an abscess aspiration or tissue from a surgical procedure.

Demographic details included age, sex and underlying conditions as risk[1-5] were recorded. Presenting sites of infection as skin and soft tissue infection, necrotizing fasciitis, upper respiratory tract infection, pneumonia, pyelonephritis, arthritis, osteomyelitis, central nervous system infection or infective endocarditis were reviewed. The criteria for necrotizing fasciitis and STSS were taken from JAMA 1993[9] (Table 1). Severity at the time of admission was assessed such as fever, hypotension (systolic BP <90 mm Hg), multiple organ failure or STSS. Investigations including complete blood count, coagulogram, blood chemistry, culture and antibiotic sensitivity of streptococcus group A and recorded. Outcome of patients was recorded as improved, survived or dead.

Statistical analysis used the chi square test and logistic regression model to determine clinical characteristics, mortality rate and prognostic factors of invasive streptococcal group A infection and STSS.

RESULTS

Overall, 540 specimens gave a positive culture for streptococcus group A. 176 patients had all inclusion criteria of invasive streptococcal group A. The mean age was 36.5 years (range 1-97). A high incidence of infection was found in children and seniors, and was lowest in the 31-40 year age group (Fig. 1). 123 patients had a previous underlying condition (69.89%). The most common was cancer (18.8%), followed by other conditions such as DM, history of steroid use and smoking (Table 2). There were only 5 patients positive for anti- HIV, however, this test was not routinely done on all patients.

Community acquired infection was more common than hospital acquired,159 patients (89.9%) compared with 17 patients (10.1%), respectively. Presenting sites were most commonly skin and soft tissue infections (Table 3). Fever or body temperature more than 37.8°C was detected at the time of admission in 140 patients (79.6%). The mean body temperature was 38.5°C. Three patients were admitted with hypothermia (body temperature <36°C), and all of them died.

Positive culture specimens were 75.6 per cent from pus and body fluid (pleural fluid and ascites), 8 per cent from tissue biopsy, 3.4 per cent from bone and 1.7 per cent from CSF. Hemoculture was performed on 102 patients, with positive results in 40 patients (39.1%).

Overall mortality from invasive streptococcal group A infection was 9.1 per cent. The authors

Table 1. Streptococcal toxic shock syndrome (STSS): Case definition.

Streptococcal toxic shock syndrome (STSS)

1. Isolation of Group A Streptococcus
   - A. From a sterile body site
   - B. From a non-sterile body site
2. Clinical signs of severity
   - A. Hypotension and
   - B. Clinical and laboratory abnormalities (≥ 2)
     1. Renal impairment
     2. Coagulopathy
     3. Liver abnormalities
     4. Acute respiratory distress syndrome
     5. Erythematous rash
     6. Extensive tissue necrosis, i.e. necrotizing fasciitis

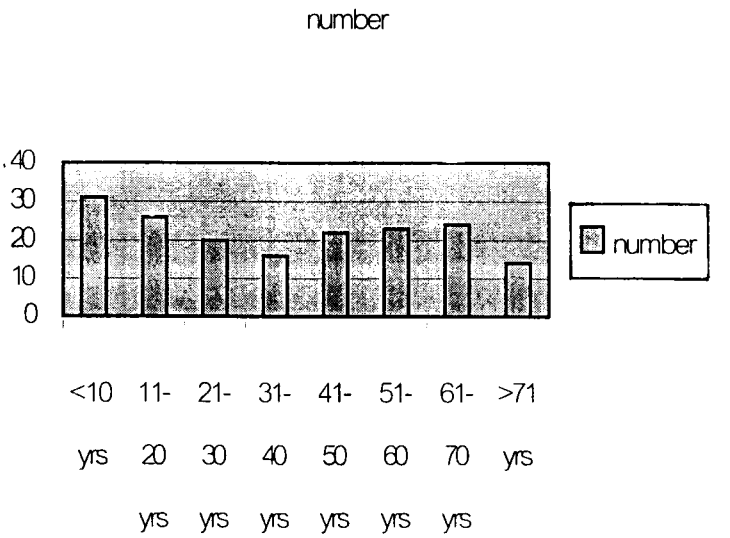
Definite case = 1A + 2 (A + B)
Probable case = 1B + 2 (A + B)

Group A streptococcal necrotizing fasciitis

Definite 1+2+3
1. Necrotizing of soft tissue with involvement of the fascia
2. Serious systemic disease including one or more of the following :
   - Death
   - Shock (Systolic pressure <90 mm Hg)
   - Disseminated intravascular coagulopathy
   - Failure of organ system (respiratory failure, liver failure, renal failure)
3. Isolation of GAS from normally sterile body site

Suspected 1+2+ Serologic diagnosis of GAS (ASLO or DNAse B)
1+2+ Histologic confirmation of gram-positive cocci in a necrotic soft tissue infection

(JAMA 1993; 269: 390-1)



Note : yrs = years

Fig. 1. Association between age and streptococcal group A infection.

Table 2. Underlying diseases.

Underlying disease	Number (case)	Per cent
Cancer	32	18.8
DM	21	12.4
Steroid use	17	10.0
Smoking	11	6.5
Cancer chemotherapy within 4 weeks	10	5.9
Skin ulcer or disease	10	5.9
Alcoholic drinking	9	5.3
Surgery within 3 weeks	9	5.3
Nephrotic syndrome	7	4.0
Vulvular heart disease	4	2.4
Chronic renal failure	3	1.8
Cirrhosis	3	1.8
Intravenous drug abuse	2	1.2
Bed ridden	2	1.2
Chronic obstructive pulmonary disease	1	0.6
Herpes skin infection	1	0.6
Total	123	69.9

Table 3. Location of infection (Presenting site).

Presenting site	Number (cases)	Per cent
Skin and soft tissue	141	80.1
Necrotizing fasciitis	16	9.1
Bone (osteomyelitis)	12	6.8
Upper respiratory tract infection	5	2.8
Arthritis area	4	2.3
Central nervous system	4	2.3
Upper urinary tract	3	1.8
Lungs (Pneumonia)	1	2.6
Unknown	8	4.5

Table 4. Organ failure in STSS patients.

Organ failure	Number (cases)
Acute renal failure	8
ARDS	8
Acute liver failure	4
Skin rash	4
Coagulopathy	4
Necrotizing fasciitis	3
Total	12

found 12 patients (6.8%) with STSS, 8 patients with skin and soft tissue infections, 2 patients with necrotizing fasciitis and 2 patients with an unknown primary infection site but positive hemoculture. Details of multiple organ failure in STSS patients is shown in Table 4. When diagnosed with STSS, the mortality rate was extremely high (50%).

Of the 176 patients, 106 patients (60.9%) were treated with a single antibiotic, cloxacillin was the most common antibiotic of choice (39.1%). Combination antibiotics, usually beta-lactam groups and aminoglycoside groups, were given to 57 patients (22.8%). Metronidazole was used in 10 patients (5.8%) as a combination drug, {nine patients (3.2%) used metronidazole combined with aminoglycoside with poor results}. Clindamycin was used in 5 patients {2 who did not have STSS (1 patient died), 3 patients had STSS (2 patients died)}. There has been no strain of streptococcus group A resistant to beta-lactam antibiotics in this series (140 tests).

By univariate analysis, the prognostic factors that increased the mortality rate from invasive streptococcal group A infection were age >65 years, body temperature <36°C, DM, systolic blood pressure <90 mm Hg, STSS, renal failure, liver failure, ARDS, positive hemoculture, positive culture from body fluid and white blood cell counts (WBC) from CBC <4,000 or >10,000/mm^3. After multivariate analysis by logistic regression, only DM (odds ratio 9.67, $p<0.025$, 95% CI 1.33-70.22), history of steroid use (odds ratio 11.17, $p<0.017$, 95% CI 1.53-81.5), STSS (odds ratio 22.16, $p<0.005$, 95% CI 2.5-196.71) and had received cancer chemotherapy (odds ratio 115.19, $p<0.003$, 95% CI 5.18-2,561.61) still significantly increased the mortality rate.

Concerning STSS, univariate analysis revealed that predictive factors for this condition were body temperature less than 36°C, positive hemoculture, and WBC <4,000 or >10,000 mm^3. Predictive factors for STSS could not be identified by multivariate analysis, however, protective factors for STSS were revealed by multivariate analysis to be age more than 65 years (odds ratio 0.02, $p<0.0001$, 95% CI 0-0.14) and steroid use (odds ratio 0.07, $p<0.027$, 95% CI 0-0.75).

DISCUSSION

Invasive streptococcal group A infection is an important medical problem in southern Thailand. Although the present study did not assess the exact prevalence of this infection, Songklanagarind Hospital has about 40 cases annually.

Most patients are under 20 or over 50 years of age, similar to other previous reports[1-5]. Almost

Table 5. Comparison between previous reports of STSS and mortality rates of streptococcal group A infections.

Report	Year (cases)	Number	STSS (%)	STSS mortality (%)	Total mortality (%)	Risk*
Ontario[2]	1992-3	323	13	81	15	STSS, NF, age
Atlanta[4]	1994-5	183	14	48	14.4	STSS, age, UK
Madrid[3]	1985-94	103	9	66	12	M1, 2, STSS
Sweden[5]	1987-95	153	13	47	11	Age, Im, STSS
Khorat[6]	1986-91	53	4	50	45	Shock, RF
Songkhla	1995-99	176	6.8	50	9.1	Steroid, Im, STSS, DM

Note : * = Mortality risk of streptococcal group A infection, STSS = Streptococcal toxic shock syndrome, NF = Necrotizing fasciitis, UK = Unknown primary site, Im = Immunosuppression, RF = Renal failure, DM = Diabetes mellitus, M1, 2 = M protein antigen type 1, 2

all patients had an underlying condition, but healthy persons, can also become infected. Skin and soft tissue were the most common sites of infection. Most patients had some degree of fever, but if they had hypothermia, as in 3 patients in this report, death is the probable outcome.

Overall mortality of invasive streptococcal group A infection in the present study was 9.1 per cent similar to others[1-5] (Table 5). One study in Thailand by Pongrithsukda W, et al reported a higher mortality rate (45% from 53 patients), which might be due to a different study population, because only positive hemoculture patients were included in their study.

DM and history of steroid use associated with increased mortality in streptococcal group A infection cases may be from reduced immunity. DM patients had abnormal phagocytic activities of the WBC (including chemotaxis, phagocytosis, ingestion and intracellular killing). Peripheral neuropathy and vasculopathy in DM also predisposed the patient for infection of the extremities. Steroid use can suppress humoral immunity and phagocytic activity. Cancer chemotherapy also led to increased mortality[3]. The present study had different results which might be due to the small number of patients who received cancer chemotherapy (5.9%).

STSS in the present study was 6.8 per cent, slightly less than in other reports (Table 5). But once STSS was diagnosed, it correlated with a 50 per cent mortality rate which was similar to the others[3-6]. No predictive factor for the increasing rate of STSS despite WBC>10,000/mm^3 showed correlation, but not significant. Conversely, when skin and soft tissue infections or necrotizing fasciitis were the infectious site, in those aged more than 65 years or with a history of steroid use, there was a significant decrease in the incidence of STSS. The interesting question is "Can using steroid on the skin and soft tissue infection including necrotizing fasciitis prevent STSS and reduce total mortality from streptococcal group A infection?". The pathogenesis of STSS was stimulation of mononuclear cells by some substances such as streptococcal pyrogenic exotoxin A and B (SPEA, SPEB), mitogenic factor (MF), streptococcal superantigen (SSA) and M protein, which produce mononuclear releasing cytokines such as tumor necrotic factor-α (TNF-α), interleukin-1B (IL-1B) and interleukin-6 (IL-6)[10]. These cytokines strongly mediate an immune response and induce abnormality and loss of permeability in vascular walls leading to hypotension after vasodilatation and leakage of intravascular fluid to the interstitium[10]. Steroids have multiple effects on immune pathways leading to decreased inflammatory responses, number of mononuclear cells, and levels of TNF-α, IL-1B and IL-6. Steroid use can prevent peripheral vasodilatation and loss of permeability in vasculature, and by these hypotheses, might then decrease STSS[15]. Old age has abnormal immune mechanisms, such as decreased number and function of T-cells lymphocyte, decreased antigen processing antigen and cytokines from macrophages[16], so eldery patients might have a lower incidence of STSS than younger patients. However, low immunity produced a high incidence of invasive streptococcal group A infection.

Different types of antibiotics had no correlation with the mortality rate in the streptococcal

group A infections or incidence of STSS. Clindamycin has been reported to suppress toxins produced by this bacteria that mediated superantigen[17]. Superantigen mediated from bacteria has been reported to produce severe inflammatory responses in animal models[18]. Some retrospective studies showed clindamycin decreased mortality[19]. So, using clindamycin combined with beta-lactam antibiotics and/or surgical removal of the source of infection were the best recommendations for treating streptococcal group A infections[19]. In the present study clindamycin was used in only 5 patients and 3 of them died. Due to the small number of patients receiving clinadamycin and because it was selected for clinical use on more severely infected patients, the authors offer no conclusions about the benefit of clindamycin. Some studies used intravenous immunoglobulin (IVIG) for treating STSS[20-22], but no patients received IVIG in the present study.

At present, the main recommendation for treatment of streptococcal group A infection is using beta-lactam antibiotics combined with clindamycin and surgical drainage. Although the present study found steroids to be a protective factor for STSS, a randomized control study is needed to test this hypothesis in the future.

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การติดเชื้อสเตร็พโตค็อคคัส กรุ๊พ เอ และกลุ่มอาการช็อคจากสารชีวพิษของสเตร็พ-โตค็อคคัส ในโรงพยาบาลสงขลานครินทร์

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ความเป็นมา : การติดเชื้อสเตร็พโตค็อคคัส กรุ๊พ เอ มีรายงานจากทั่วโลกว่าทวีความรุนแรงเพิ่มขึ้น และพบภาวะช็อคจากสารชีวพิษของเชื้อสเตร็พโตค็อคคัส ซึ่งมีอัตราตายสูงมากในประเทศไทย โดยเฉพาะภาคใต้ยังไม่มีการรายงานที่ชัดเจน

วิธีการ : รวบรวมข้อมูลจากเวชระเบียนของผู้ติดเชื้อสเตร็พโตค็อคคัส กรุ๊พ เอ ซึ่งมารับการตรวจที่โรงพยาบาลสงขลานครินทร์ ตั้งแต่ 1 มกราคม 2538 ถึง 30 มิถุนายน 2542 เพื่อศึกษาปัจจัยเสี่ยงต่อการเสียชีวิตจากเชื้อ และการเกิดภาวะช็อคจากสารชีวพิษของเชื้อชนิดนี้

ผลการศึกษา : มีผู้ติดเชื้อสเตร็พโตค็อคคัส กรุ๊พ เอ 176 ราย ร้อยละ 89.9 ติดเชื้อนอกโรงพยาบาล และร้อยละ 69.7 มีโรคประจำตัวอยู่เดิม ส่วนใหญ่ติดเชื้อที่ผิวหนังและเนื้อเยื่อใต้ผิวหนัง (ร้อยละ 80.1) อัตราตายโดยรวมร้อยละ 9.1 ผู้ป่วย 12 ราย ได้รับการวินิจฉัยภาวะ STSS ในจำนวนนี้เสียชีวิต 6 ราย ปัจจัยที่สัมพันธ์กับการเพิ่มอัตราตายคือ โรคเบาหวาน (Odds ratio 9.67, p<0.025), การได้รับยาสเตียรอยด์ (Odds ratio 11.17, p<0.017), ภาวะ STSS (Odds ratio 22.16, p<0.005), และการได้รับยาเคมีบำบัดภายใน 4 สัปดาห์ (Odds ratio 115.19, p<0.003) ไม่พบปัจจัยที่มีผลเพิ่มโอกาสเกิดภาวะ STSS แต่พบว่า ผู้มีอายุมากกว่า 65 ปี และผู้ได้รับยาสเตียรอยด์ มีโอกาสเกิดภาวะ STSS ลดลง (Odds ratio 0.02, p<0.0001 และ Odds ratio 0.07, p<0.027)

สรุป : ภาวะการติดเชื้อสเตร็พโตค็อคคัส กรุ๊พ เอ เป็นปัญหาที่สำคัญทางภาคใต้ของประเทศไทย โดยเฉพาะเมื่อเกิดภาวะ STSS จะมีอัตราตายสูงมาก

คำสำคัญ : ภาวะติดเชื้อสเตร็พโตค็อคคัส กรุ๊พ เอ, ภาวะช็อคจากสารชีวพิษของเชื้อสเตร็พโตค็อคคัส

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