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Regional outbreak of staphylococcal scalded skin syndrome in healthy children

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= Abstract =

Purpose : Staphylococcal scalded skin syndrome (SSSS) is a relatively uncommon superficial blistering skin disease that is due to *Staphylococcus aureus*. We had experienced a regional outbreak of SSSS over 3 years in healthy children.
Methods : We retrospectively reviewed the medical records of those patients diagnosed as SSSS. Most of neonatal cases were nosocomial infections and excluded from the analysis. The clinical features, laboratory findings, the isolation and antibiotic resistance of *S. aureus*, the antibiotic management and other supportive treatments were analyzed.
Results : Fifty-five patients with SSSS were admitted to our hospital from October 2001 to September 2004. The median age of patients was 3.0 years. Of the 55 patients, 9 were the generalized type, 13 were the intermediate type and 33 were the scarletiniform rash. All the patients were living in neighborhood of the Jinju area. *S. aureus* were isolated from 9 of the patients and all of the isolated S. aureus were methicillin resistant. All the patients except two were treated with intravenous flocloxacillin or nafcillin and/or cefotaxime. All the patients recovered during the follow-up period of 2 to 3 weeks.
Conclusion : We experienced a regional outbreak of SSSS in previous healthy children. Further study for finding the carriers of *S. aureus* caused SSSS and preventing the spread of this disease is needed. Additionally, guidelines for treating SSSS due to methicillin resistant *S. aureus* should be established. **(Korean J Pediatr 2010;53:48-55)**

Key Words : Staphylococcal Scaled Skin Syndrome, Outbreak, Methicillin Resistant *Staphylococcus aureus*

Introduction

Staphylococcal scalded skin syndrome (SSSS) is a relatively uncommon superficial blistering skin disease that is caused by the exfoliative toxins (ET) of *Staphylococcus aureus* (*S. aureus*)[1]. Its clinical manifestations are varied and they include the generalized, localized (bullous impetigo), abortive (scarletiniform rash) and the intermediate forms[2, 3]. The scarletiniform rash is also called staphylococcal scarlet fever, and this is generally considered to be a milder form that is characterized by fever and a generalized tender erythema without exfoliation or the formation of bullae.

The diagnosis of SSSS is mainly based on clinical appearance, and it is confirmed by the isolation of S. aureus or the exfoliative toxin (ET) and/or the histopathological findings. However, the typical SSSS presents for several days, and the generalized SSSS is a rare condition that usually occurs in neonates. Thus, a structured management approach to this disease that involves a high index of suspicion is recommended[4].

SSSS cases caused by methicillin resistant *staphylococcus aureus* (MRSA) have recently been reported both in our country and worldwide[5]. The choice of antibiotics for a community acquired MRSA skin infection has been controversial[6].

From late 2001, skin lesions presumed by bacterial infection developed persistently. Firstly, we diagnosed scarletiniform rash due to erythema, bullae, positive Nikolsky sign and itching. We investigated the prevalence of these skin lesions, and there was a mixture of generalized SSSS,

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scarletiniform rash, and bullous impetigo.

Many outbreaks of SSSS have been reported[7, 8, 10, 11]. Small outbreaks in children or a few familial outbreak cases[13] also have been reported. However, any continuing outbreak of SSSS in children over a few years had been rarely observed.

In this study, we considered clinical symptoms, antimicrobial susceptibility and regional outbreak of SSSS over a few years.

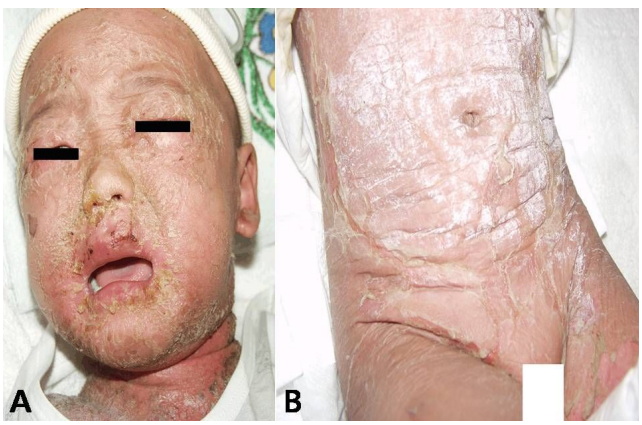

Fig. 1. Generalized Staphylococcal scalded skin syndrome (SSSS) in a previously healthy child of 27-month-old. The photograph (A and B) shows the characteristic erythematous superficial exfoliation with a positive Nikolsky sign.

Materials and methods

From Oct 2001 through Sep 2004, 72 patients from the Department of Pediatrics, Gyeongsang National University Hospital (GNUH) who were admitted and diagnosed with SSSS were identified. Hospital records and laboratory records were reviewed to obtain information, including the patients' ages, gender, site of initiation, the clinical features of SSSS, the laboratory findings, the culture and antibiotic resistance of *S. aureus*, and we also report on the proper antibiotic management and the other supportive treatments.

In this study, the localized SSSS cases (bullous impetigo) were excluded due to the fact that most of these patients were not admitted and they were managed with oral antibiotics.

The patients were classified according to three skin manifestation: the generalized type (group 1), defined as a case where there was tender erythema and large bullae involving over 30% of whole body with a positive Nikolsky sign; the intermediate type (group 2), defined as a case where there was tender erythroderma and several vesicles or pustules with a positive Nikolsky sign; and the abortive type (scarletiniform rash, group 3), defined as a case where there was tender erythema on the whole body with

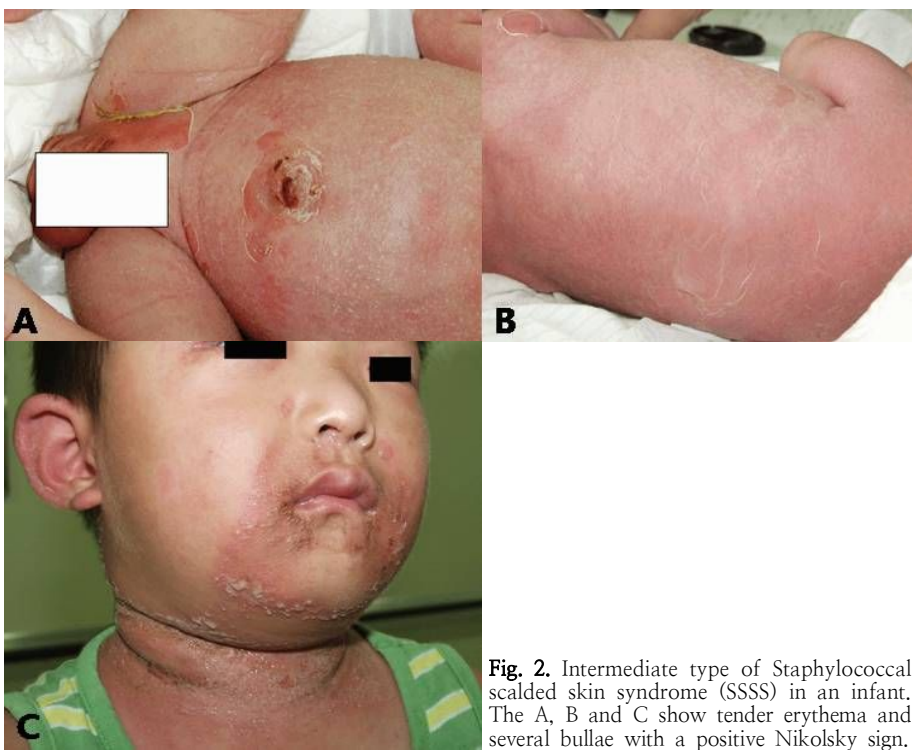

Fig. 2. Intermediate type of Staphylococcal scalded skin syndrome (SSSS) in an infant. The A, B and C show tender erythema and several bullae with a positive Nikolsky sign.

a negative Nikolsky sign (Fig. 1-3)[3].

Results

1. Prevalence of SSSS

From Oct 2001 to Sep 2004, a total of 9,891 were admitted in Department of Pediatrics, GNUH, and the patients who were diagnosed in SSSS were 0.56% (55/9,891). Annual prevalence (number of 1,000 admitted patients) was abruptly increased during Oct 2001 to Sep 2004, compared with previous annual prevalence (Fig. 4). Seventy-two patients with SSSS were admitted to our hospital from Oct 2001 to Sep 2004. Seventeen of 72 patients were neonates

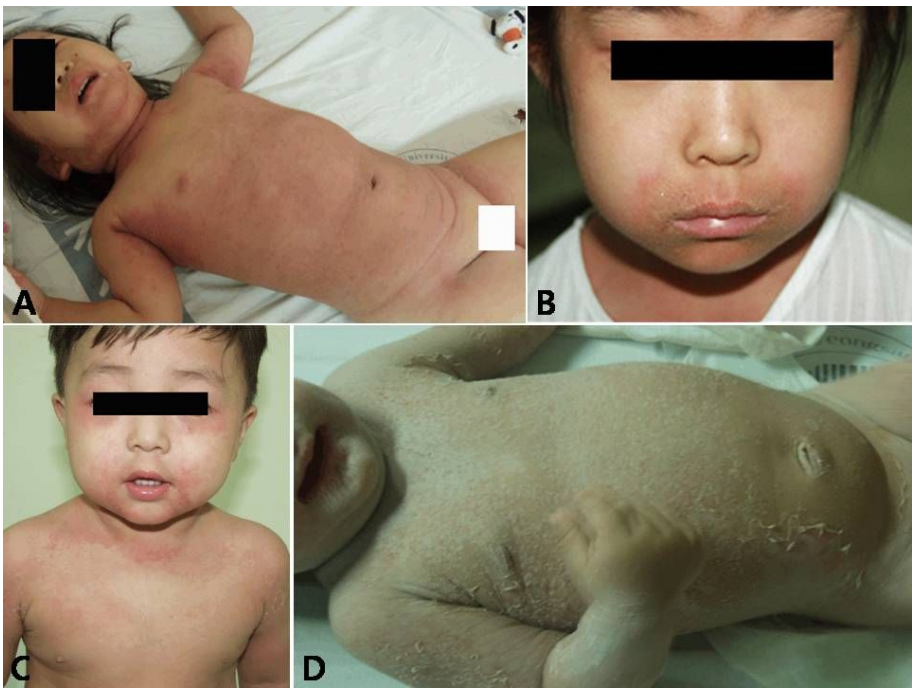

Fig. 3. Scarletiniform rash in children. The case was tender erythema on the whole body with a negative Nikolsky sign, and the erythema (A, B and C) is followed by the thick flakes over the next week (D).

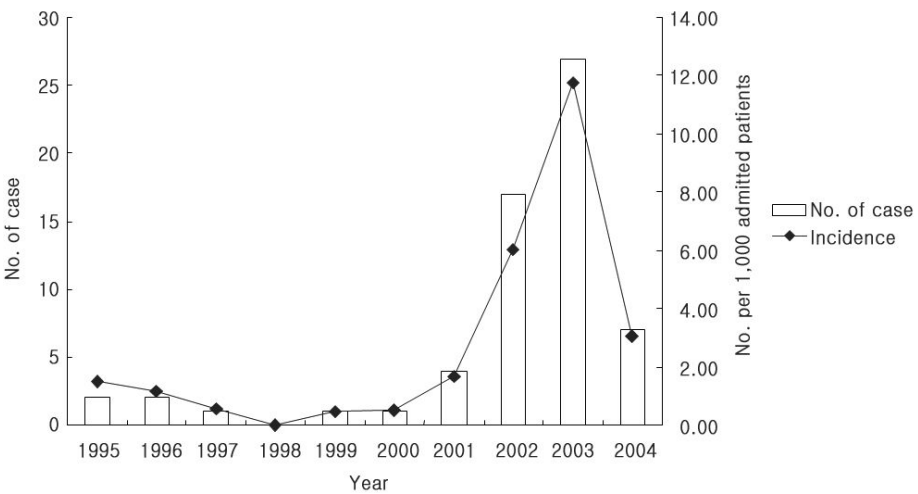

Fig. 4. Annual incidence of Staphylococcal scalded skin syndrome (SSSS). The annual incidence and number of case diagnosed in Staphylococcal scalded skin syndrome (SSSS) was abruptly increased during 2001 to 2004.

(<28 days of age) and 11 of the seventeen cases were born in same hospital, and a nursery-associated outbreak was suspected. The onset of the disease varied from 5 to 25 days after their discharge from that hospital, but these were considered as nosocomial infection, so all cases of neonates were excluded in this study.

The study group was composed of 30 boys and 25 girls (the boy:girl ratio was equal to 1.2:1). The median age of the patients was 3.0 years (range: 1 month to 8 years 8 months) (Table 1). Of the 55 patients, 9 were the generalized type, 13 were the intermediate type and 33 were the abortive type. The abortive type was 60% of all cases. The generalized type was displayed more in infants than in children 1 year old and over.

2. Clinical symptoms

Most patients had been transferred to our hospital after initial management at the local clinic was done under the clinical impression of SSSS, erythema multiforme, skin rash, toxic dermatitis, impetigo, atopic dermatitis, urticaria, food poisoning, drug rash or scarlet fever.

Most of our patients initially developed itching, a febrile sensation and irritability, and this was followed by a generalized, tender erythematous rash, which generally begins on the head and neck. The initial lesion looked like impetigo around the eyes, nose and lips. The rash spread to the rest of the body from the head to the lower extremities within a week.

For the patients with the scarletiniform rash, the erythroderma with sandpaper-like texture was followed by thick flakes developing within a few days and the entire skin desquamated over the next 2 or 3 weeks.

Twelve (21%) of the total patients had fever (body temperature ≥38℃) that subsided within 2 days, but 43 patients had a febrile sensation without fever.

There were variable coexisting diseases: rhinitis, acute pharyngitis, conjunctivitis, acute otitis media, gastritis, pneumonia and sepsis.

For one case who was one-month-old girl, she was twice admitted in diagnosis of generalized SSSS. In first admission, she was transferred to our hospital under impression of collodian baby, and managed with intravenous flocloaxcillin for 7 days. The blood culture was positive of *S. aureus*. In fifth day after discharge, she was readmitted as same symptom and managed with vancomycin for 7 days.

Table 1. Age Distribution and Clinical Subtypes of Children Diagnosed as Staphylococcal Scalded Skin Syndrome

Age (yr)	Group 1	Group 2	Group 3	Total
<1	4	1	1	6
1-2	1	1	5	7
2-3	0	4	8	12
3-4	3	5	8	16
4-5	1	1	4	6
>5	0	1	7	8
Total	9	13	33	55

Group 1 : The generalized type
Group 2 : The intermediate type
Group 3 : The abortive type (scarletiniform rash)

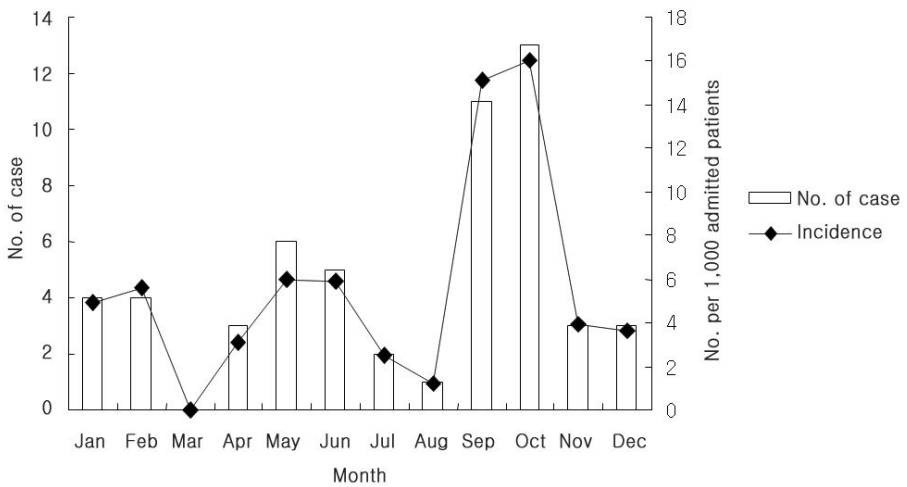

Fig. 5. Monthly incidence of Staphylococcal scalded skin syndrome (SSSS). This figure showed that high prevalence in Sep and Oct.

3. Prevalence and regional distribution

The annual prevalence was 4 cases in 2001 (Oct to Nov), 17 cases in 2002, 27 cases in 2003 and 7 cases in 2004 (Jan to Sep), respectively. The monthly prevalence was 4 cases in Jan, 4 cases in Feb. 0 case in Mar, 3 cases in Apr, 6 cases in May, 5 cases in Jun, 2 cases in Jul, 1 case in Aug, 11 cases in Sep, 13 cases in Oct, 3 cases in Nov, and 3 cases in Dec (Fig. 5).

All the patients were living in neighborhood of the Jinju area: Jinju 31, Sacheon 6, Tongyeong 6, Sancheong 1, Geoje 3, Goseong 2, Masan 2 and Hadong 4.

4. Laboratory findings

The WBC count was slightly elevated (mean: 10,432/mm^3) with little or no shift in the differential count. No differences among types of SSSS were present. The levels of C-reactive protein were not increased except one patient (23.8 mg/L). The results of the liver function tests, electrolytes and serum creatinine were within the normal limits at the time of admission.

In 9 of the total patients, *S. aureus* was isolated from culturing the throat or the wound site. All of the S. aureus in these patients was resistant to methicillin. The MRSA was susceptible to ciprofloxacin, nitrofurantoin, rifampin, tetracycline, vancomycin and trimethoprim/sulfamethoxazole. Compared with the nosocomial MRSA isolated from our hospital, this MRSA was sensitive to ciprofloxacin, tetracycline and trimethoprim/sulfamethoxazole (Table 2).

Table 2. The Results of Antibiotic Sensitivity Test of *Staphylococcus aureus* isolated from Patients diagnosed as Staphylococcal Scalded Skin Syndrome

Antibiotics	MIC (μg/mL)	Sensitivity
Cephalothin	≥32	R
Ciprofloxacin	≤0.5	S
Clindamycin	≥8	R
Erythromycin	≥8	R
Gentamicin	≥16	R
Nitrofurantoin	≤32	S
Oxacillin	≥8	R
Penicillin-G	≥16	R
Rifampin	≤1	S
Teicoplanin	≤4	S
Tetracylcine	≤1	S
Trimthoprim/Sulfamethoxazole	≤10	S
Vancomycin	2	S

Abbreviation : R, resistant; S, sensitive; MIC, minimal inhibitory concentration

For one patient who was diagnosed with sepsis, MRSA that had identical antibiotic susceptibility results was isolated from both the blood culture and culture of the periorbital pyoderma.

5. Response to treatment

All the patients except two cases were treated with intravenous flocloxacillin or nafcillin and/ or cefotaxime (7 days). In one patient with *S. aureus* sepsis, the fever and formation of bullae persisted for 7 days and so the antibiotics were changed to vancomycin. In the other patient who readmitted after discharge, she was treated with vancomycin. Topical antibiotics [Bactroban® (Mupirocin), Hanall Co., Seoul, Korea] were applied on the pyoerythema, especially on the perioral area or around the nose. Any eye discharge and conjunctival injection were managed with erythromycin eye ointment (Ecolicn®, Tae Joon Pharm, Seoul, Korea). Burrow's solution and 40% zinc oxide ointment were used for the tender erytheroderma. In most of the patients, their fever subsided within 2 days. Within 5 to 7 days, the erythema begins to resolve, and this was followed by desquamation from the head, neck and trunk to the lower extremities. The pyoderma and formation of bullae improved within 3 to 5 days.

There were no complications or deaths, and the prognosis was good. At the 2 or 3 week follow up, all the patients had recovered without sequelae.

Discussion

We report here on an epidemic of staphylococcal scalded skin syndrome in healthy children. Previously there were no endemic or epidemic outbreaks of SSSS in Jinju area.

The rate of scarletiniform rash was 60.0% (33/55). The diagnosis of the first patient was difficult due to the fact that there was no associated fever, and scarletiniform rash is a rare form of SSSS. Scarletiniform rash, also called staphylococcal scarlet fever, or the abortive form of SSSS has generally considered as the milder forms of this disease. Patients usually develop a generalized tender erythroderma with a roughened, sandpaper-like texture, and this is associated with fever, but in our patients, there was no associated fever. Unlike the generalized SSSS, bullae did not develop. The scarletiniform rash was very difficult to differentiate from other causes of infectious erythroderma such as toxic shock syndrome (TSS) and streptococcal

scarlet fever[3, 9].

Most of the SSSS outbreak developed among the newborn who were cared for by an asymptomatic carrier of ET-producing *S. aureus* with generalized SSSS. Curren[10] et al. reported on an outbreak of neonatal SSSS, and 35.3% of the cases had generalized exfoliative dermatitis, and 11.8% of the cases had staphylococcal scarlet fever. In our study, the cases of generalized SSSS were 4 of 6 (66.7%) infants who under 1 year old, and 5 of 49 (10.2%) in children aged 1 year and older. The number of scarletiniform rash was increased with age. In 1976, a nursery outbreak of scarletiniform rash caused by phage group I *S. aureus* was reported[11]. Yet in our study, we did not collect the isolated bacteria and we didn't evaluate the exfoliative toxin or phage group.

The diagnosis of SSSS is usually based mainly on the clinical manifestations, and the diagnosis is supported by the presence of *S. aureus* in the nasal, conjunctival, pharyngeal or wound swabs. Several risk factors of SSSS have been suggested: poor renal clearance of the toxins, low antibody status, immunosuppression with immunosuppressive drugs and malignancy[3]. In our study, most of the patients were preschool-aged children who were relatively healthy and they were not immunocompromised, and they had no chronic illness or renal disease. We did not examine the serum antibody titers against *S. aureus*. SSSS has recently been described in an individual taking a nonsteroidal anti-inflammatory drug (NSAID). These drugs promote *S. aureus* growth and decrease renal clearance of the toxin[9]. In our study, no patient had been managed with NSAIDs, but some of our patients were managed with oral prednisolone under impression of Stevens-Johnson syndrome or atopic dermatitis before their transfer to our hospital.

In neonates and children, transmission of the exfoliative toxin-producing *S. aureus* appears to occur through asymptomatic carriers[8]. Community-acquired MRSA infections have been increasingly reported among athletes and in the army. For a college football team, MRSA was spread predominantly during the practice play with skin breaks facilitating infection; hence, it is important to screen for potential carriers[12]. In our study, we did not prove that direct contact occurred with an asymptomatic carrier, or that the infection was due to previous hospital management. Some children denied a direct contact history with patients having skin lesions. Ladhani and Newson[13] reported the case of a familial outbreak of SSSS and they suggested the importance of identifying and treating the close infectious contacts of the patients with generalized SSSS. In our study, two patients were siblings, and this suggested that SSSS is contagious disease. However, no other family including children and adults developed SSSS or impetigo. Culture for the other family was not performed in out study. Yet in our cases, there were no evidence of disease propagation to other children in the same room, and most of the children played together in the kindergarten.

During the 3-year study period, 55 cases of SSSS occurred with 9 cases (16.4%) of isolated *S. aureus* being seen on the culture study. The low positive number of culture studies was perhaps due to that most patients had undergone previous antibiotic treatment. Cultural data was available for 9 patients, and all were positive for MRSA, but further testing for typing the *S. aureus* could not be done. In our country, SSSS due to MRSA has been reported and this was managed with intravenous vancomycin[14]. We used vancomycin in only two cases. The cultural reports were usually ready after 3 to 5 days, and the patients who had positive culture for MRSA did not have their antibiotics changed.

The prompt diagnosis and early treatment for this disease is important. In treating SSSS, the parenteral antibiotics such as flocloxacillin would be recommended except for localized SSSS, which is managed with a topical agent and oral antibiotics that cover both staphylococci and streptococci. Any blisters should be left intact. The eroded areas are best covered with white petrolatum-impregnated gauze that helps reduce further trauma to the skin. A topical antibiotic or antiseptic eye ointment is helpful to manage the eczema around eyes and lips[1]. In our study, we could not rule out scarlet fever for the first patient because the skin lesions looked like scarlet fever, and the patient was without any definitive fever. So, a combination of cefotaxime and flocloxacillin was used. In our hospital, wet gauze with Burrow solution was applied on the blistered skin and tender erythema, and 40% zinc oxide ointment made in our hospital was used on the scareletiniform rash. Bactroban® (mupirocin) ointment was used on the impetigo-like lesions around the lips and nose, and on the erosion on the flexural areas (neck, axilla and inguinal areas). Severe periorbital lesion was managed with eye ointments containing antibiotics such as colimycin® (Hanil Parm, Seoul, Korea) or ecolicin®.

Within 2 to 3 days, the fever usually subsides, the erythema begins to resolve and there is no new bullae forma-

tion. Because the antibiotics are targeted to the offending organism, the exofoliation will continue for another 24 to 36 hours after the start of antibiotic administration. The desquamation of the skin generally occurs 3 to 5 days after disease onset, and complete resolution occurs in most cases, usually within 2 to 3 weeks with no permanent sequelae[1, 3]. The facial edema, periorbital eczema, erythema and erosion were improved within 3 to 4 days. However, the desquamation developed from head to the leg and this persisted for 2 to 3 weeks. All 55 patients improved without scarring on the out-patient department follow-up.

There are several limitations for our study. First, we did not do further study to find out the origin of the disease, such as taking throat or nasal cultures for *S. aureus* from the adults around the patients. So, we could not explain the spread pathway of *S. aureus*. Second, the isolated MRSA was considered as contaminated bacteria in some patients, and further study for the phenotyping or the isolation of the exfoliative toxin could not done. Third, as all the outbreak patients were not included in our study, the accurate number of SSSS patients remains unknown.

In summary, we report here on a regional outbreak of SSSS in previous healthy children. However, we did not prove the mechanism of bacterial transmission. If SSSS develops persistently in a population, then further study for finding the MRSA carriers and preventing the spread of this disease are needed. Additionally, guidelines for treating SSSS due to MRSA should be established.

한 글 요 약

건강한 소아에서 포도알균화상피부증후군의 지역적 유행

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도현정 · 박은실 · 임재영 · 박찬후 · 우향옥 · 윤희상 · 서지현

목 적: 포도알균화상피부증후군(4S)은 황색 포도알균과 관련된 표재성 수포가 생기는 거의 드문 피부 질환이다. 저자들은 3세 이상의 건강한 소아에서 4S의 지역적 유행을 경험하였다.

방 법: 저자들은 4S를 진단받았던 환아들을 대상으로 의학적 기록을 후향적으로 분석하였다. 신생아들의 경우 외인성 감염이 대부분이었으므로 이 연구에서 제외되었다. 임상적 특징, 실험 결과, 황색 포도알균의 항생제 내성과 분리, 항생제 치료와 보존적 치료법을 분석하였다.

결 과: 2001년 10월부터 2004년 9월까지 본원에 입원하였던 4S를 진단받은 55명의 소아들을 대상으로 하였다. 환아들의 평균 나이는 3세였다. 55명의 환아 중에서 9명이 전신형, 13명이 중간형이었으며 나머지 33명이 성홍열모양 피부발진이 있었다. 모든 환아들은 진주의 인접한 지역에 살고 있었다. 황색 포도알균은 9명의 환아에서 분리되었고, 분리된 모든 황색 포도알균은 methicilline 저항성을 가지고 있었다. 2명을 제외한 환아들은 flocloxacillin 또는 nafcillin 또는 cefotaxime 정맥 주사로 치료하였다. 모든 환아들은 2-3주간의 추적 기간 동안 완전히 회복되었다.

결 론: 저자들은 이전에 건강했던 소아들에서 4S의 지역적 유행을 경험하였다. 이 질환의 유행을 막기 위해서 4S를 일으키는 황색 포도알균의 매개체를 찾기 위한 더 많은 연구가 필요하다. 부가적으로 methicilline 저항성 황색 포도알균이 많으므로 4S를 치료하기 위한 지침서가 확립되어야 할 것으로 사료된다.

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