Epidemiological Study of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Retrospective Analysis of Southern Taiwanese Population During 2002 to 2007

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\textbf{Background:} Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe adverse drug reaction with potentially life-threatening skin disease. The widely accepted consensus regarding therapy does not exist at present and epidemiological data of Taiwan in recent years is limited.

\textbf{Objective:} To evaluate the efficacy of systemic steroid therapy in treatment of SJS and TEN and also analysis the associated epidemiology data.

\textbf{Methods:} This study was performed by retrospectively chart review of patients admitted with SJS or TEN in a tertial referral medical center in southern Taiwan between 2002 and 2007. Clinical data including mortality, morbidity, the category of offending drugs and the systemic steroid treatment effects were analyzed.

\textbf{Results:} Total 52 patients were included; 10 were classified as TEN and 42 as SJS. Overall mortality is 3.8\% and infectious morbidity is 23\%. In aspect of causative agents, anticonvulsants (especially carbamazepine) were the most common drugs followed by Non-Steroid Anti-inflammatory Drugs, allopurinol and antibiotics in our series. Early systemic steroid administration may shorten the hospitalization duration than supportive care ($p < 0.012$) in our study.

\textbf{Conclusion:} In our study, early administration of systemic steroids maybe benefits in the forms of inflammation prevention and disease progression. Short-term use to preclude infection morbidity, as well as a tapering dose as soon as possible, is suggested. (Dermatol Sinica 27: 15-26, 2009)

\textit{Key words:} Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), Clinical outcome, Systemic steroid

\textbf{INTRODUCTION}

Skin manifestations are the most common clinical feature of adverse drug reaction. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), in their severe forms, are characterized by detached necrotic epidermis and mucosa involvement.\textsuperscript{1} In fact, adverse drug reaction is the leading
cause of said manifestations in SJS-TEN group. Antibiotics (especially sulfonamide) were most frequently prescribed in English literature from 1995 to 2002, followed by analgesic-nonsteroidal antiinflammation drugs (NSAID) and anticonvulsants. Currently, reports in Europe and Israel point to allopurinol being the most commonly used due to restrictions on cotrimoxazole use and allopurinol’s new indications in cardiovascular disease in recent years. Changes to offending drugs in the evolution of medical practice guidelines are somewhat predictable, and susceptibility to adverse drug reaction varies across different races. Anticonvulsant, especially carbamazepine reportedly place Han Chinese individuals at higher risk for SJS and TEN. To the best of our knowledge, epidemiological data of SJS and TEN in Taiwan have been scarce and rarely up-to-date. Current management strategies are based on medication related specific immune mechanism but benefits of systemic steroid treatment are still controversial due to a lack of randomized-control study evidence. There are also few treatment experience reports of SJS/TEN group in Taiwan.

In this investigation, we retrospectively assess the hospitalization cases of SJS and TEN within five-year period. The clinical outcomes, possible offending agents, pathological findings, hospitalization duration, laboratory exams, mortality, morbidity and treatment effects were analyzed.

**MATERIAL AND METHOD**

A retrospective study was performed. Of cases admitted to the general dermatology ward or burn center of our tertial referral medical center in southern Taiwan between January 2002 and August 2007. The medical records—including probable offending drugs, hospitalization duration, pathological change, treatment course, associated laboratory examinations and morbidity were obtained for these patients.

In general, the diagnostic criteria of SJS and TEN are based on rapidly expanding, erythematous or purpuric macules with the involvement of more than one mucosa site (Fig. 1) (oral, conjunctiva, anogenital). In latter, the skin rash confluence is more widespread and a dusky detachment of epidermis can be found. The characteristic differentiating SJS from TEN is based on body surface area (BSA); SJS is defined as BSA < 10%, SJS-TEN overlap syndrome 10-29%, and TEN was defined as BSA > 30%, according to updated consensus criteria used in the European SJS consortium. In our series, we classified SJS and SJS-TEN overlap syndrome as SJS, due to the rarity of such cases, with BSA < 10%; there was rarely a need for admission therapy in our hospital. Constitutional symptoms—such as fever at the time of admission were thoroughly varified. Prodromal fever was defined as a body temperature higher than 38°C before or during initial admission.
The probable offending drugs were defined according to the following criteria: (1) medications were taken within one month prior to the episode and were compatible with the chronology of skin rash; (2) patients had a previous similar adverse skin reaction history after taking the same drug, and (3) if many possible drugs were reportedly used concurrently, the most common offending drug, as cited in the English literature was suspected. An infection survey is performed on patients with persistent fever—even when there was no further progression of skin lesions—as well as those with clinical infection related signs and symptoms. Wound, urinary, and septic infections were confirmed by positive culture reports; oral candidiasis was confirmed by typical clinical presentation or positive KOH scraping. Laboratory exam findings, including liver function and CRP data were collected for most patients. Any patient with liver function up to two times greater than the normal upper limit was considered a significantly abnormal case.

There were three different treatment strategies: supportive care only, systemic steroid only and combined systemic steroid with prophylactic antibiotics treatment. The dose of systemic steroid was presented at maximum dose (usually the initial dose). An antibiotic prescription for patients without an obvious infectious focus at admission was defined as prophylactic use. Empiric antibiotics were prescribed to patients with confirmed infectious focus.

We also reviewed the pathological reports of the patients in our study. Total hospitalization duration was analyzed and cases were categorized by disease severity, infection morbidity and treatment group. Two deceased patients and one admitted due to poor wound—healing were excluded from the analysis of hospitalization duration due to the extremely short hospitalization times involved.

Demographic data such as age, hospitalization duration, laboratory data, pathological findings, mortality and morbidity were...
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calculated as descriptive statistics (i.e. mean, percentage). Hospitalization duration differences according to different disease severity (SJS vs. TEN), infectious morbidity, and different treatment groups were calculated with Statistics Package for Social Science (SPSS) software, version 12.0 (SPSS Inc. Chicago, IL, USA) with the significance level set to p<0.05. The statistical analysis of difference in hospitalization duration was performed using Kruscal-Wallis test and a Wilcoxon-rank-sum test.

RESULTS

In total, 52 patients with SJS or TEN were included in this series; the clinical characteristics of SJS and TEN are listed in Table 1. The mean age of the SJS-TEN patients was 52 ± 18 year-old (range 18~81 years) and the gender ratio was 1:1 in our series. Overall, the average hospitalization duration was 12.4 days (with the exclusion of the 3 cases mentioned above). Two patients had died; both had been classified as TEN. Each of these two cases had also a history of delayed diagnosis, and one had primitive visceral organ failure disease.

Liver function was elevated in about half the patients (22/52, 52.3%) during hospitalization; the means of AST and ALT were 59.95U/L (normal range 0~37) and 71.5 U/L (normal range 0~40), respectively. The highest levels within any single patient were an AST value of 401 U/L and an ALT value of 651U/L. Most of the elevated transaminase enzyme levels were between one- and two-fold the normal upper limits. CRP was also checked in 21 patients with the mean and median thereof being 83.65 mg/L and 60 mg/L (normal range < 5), respectively; only two cases were within normal range. Only half the patients with a confirmed infection had an obviously elevated CRP value.

The most common causative drugs in our hospital are listed in Table 2. Anticonvulsants (especially carbamazepine) were

<table>
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<th>Table. 2 Possible Offending Drugs of SJS and TEN in Our Study</th>
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<td><strong>Offending drugs</strong></td>
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<tr>
<td>Antibiotics*</td>
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<tr>
<td>NSAID</td>
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<tr>
<td>Allopurinol</td>
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<tr>
<td>Anticonvulsant</td>
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<tr>
<td>Carbamazepine</td>
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<tr>
<td>Phenytoin</td>
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<tr>
<td>Lamotrigine</td>
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<tr>
<td>Chinese herbal medicine</td>
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<tr>
<td>Others</td>
</tr>
<tr>
<td>Unknown</td>
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</tbody>
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\* Each one of antibiotics: clindamycin (1), cephalaxin (1), cotrimoxazole (1)
*Chlorpropamide
# Benzodiazepam
the most common offending drugs in our hospital, followed by NSAID and allopurinol. Table 3 lists the underlying disease that justify the use of offending drugs. Among our patients, numbness—such as that from degenerative arthritis or peripheral neuropathy—was the main indication for carbamazepine use. The use of antibiotics such as sulfonamide was not common in our series; only one case was noted.

Thirty-one patients (59.6%) had an infection survey. Infection morbidity was confirmed by typical clinical presentation or positive culture results. Seven cases had positive wound cultures and only two cases had sepsis with positive blood cultures. One sepsis patient had the same pathogen in both wound and blood cultures; skin wound bacteria translocating to blood through a defective skin barrier was highly suspected. Urinary tract infection was also noted in two patients; both had had positive urinary analyses and culture reports. One case of pneumonia was diagnosed by chest plain-film exam. The overall infection morbidity was 23%. Regarding the use of prophylactic antibiotics, 10 of 12 infected patients had received systemic steroid therapy. Additionally, six of 47 patients who had received systemic steroid had oral candidiasis, compared to only one case in the non-steroid treatment group during hospitalization. The two patients with sepsis had each received systemic steroid therapy during admission.

Skin biopsies were performed for only 15 patients (28.9%) and pathology sections were reviewed. The histological findings for all patients mainly consisted of basal layer vacuolar change; a variable number of dyskeratotic cells in the epidermis; and superficial, mostly perivascular, mononuclear cells infiltration (Fig. 2). Degree of severity varied, from a few dyskeratotic cells to whole layer epidermal necrosis and from an interface change to subepidermal bulla formation; this severity was not well correlated to clinical severity. Most cases showed a flattened rete ridge and a moderate to severe perivascular mononuclear cells infiltration. In addition, two cases each presented superficial, deeper, and peri-appendageal involvement. However, accompanying eosinophils infiltration was rarely noticed. Other less common findings included: papillary dermis edema, extravasations erythrocytes and spongiotic change over epidermis.

Patients were further subdivided into three groups, according to their treatments. Four patients received supportive care only,
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33 received systemic steroid only, and 10 patients received both prophylactic antibiotics and systemic steroid. Empiric antibiotics were prescribed for six patients who initially presented with urinary tract infection and cellulitis. The average initial steroid dose was hydrocortisone 275 mg per day (range: 25~600 mg; median: 300 mg). All patients had gradually tapered steroid dose during hospitalization.

The mean hospitalization duration of each treatment group is shown in Table 4. The duration was longest for the combined antibiotics and systemic steroid group, followed by the supportive care, and steroid-only group. The duration differences among the therapy group were statistically significant (p = 0.012). In our series, the patients within systemic steroid therapy group had shorter hospitalization times than those in the supportive care, and the TEN patients had obviously longer admission times than those with SJS (p = 0.002). All infection cases had longer hospitalization durations than cases without infection (p = 0.021). Additionally, intensive burn center care was provided for seven patients and five of them were TEN. Extensive sloughing of skin with difficult general ward wound care was the major indication in these patients for burn center care, but another two patients with severe respiratory distress and sepsis complications after admission were later transferred to the burn center for intensive monitor and respiratory ventilator support. The benefits of intensive burn center care cannot be determined via our study, due to the small sample sizes involved in each group and difference in transfer times.

Late sequela of mucosa scarring, especially ocular mucosa, was followed up after discharge. Eight of 50 survival patients (16%) needed more ophthalmology department follow-up and one patient was recorded as having oral mucosa scarring. The complications of ocular mucosa were including: blurred vision with corneal scarring (N=3), symblepharon (N=2), entropion (N=1), chronic blepharoconjunctivitis (N=1) and photophobia (N=1).

**DISCUSSION**

Both SJS and TEN are potentially life-threatening conditions. The mortality rates vary in different reports. A multinational case-control study of Europeans (SCAR
study, 1989-1995) showed mortality rate of 1~3% and 6~39% for SJS and TEN, respectively, which aligns with our data: 0% and 20% for SJS and TEN, respectively. The estimated disease incidence of SJS-TEN in general population of southern Taiwan (including the Kaohsiung and Ping-tung areas) in our hospital is 2.8 cases per million, per year. The real incidence may be underestimated, however, due to the facts that we are not the sole medical center in Kaohsiung and that some patients received treatment in out-patient department. The increasingly intensive hospitalization care rate, together with adequate management and supportive care guidelines in recent years may have play roles in lowering mortality rate.

The only two cases with fatal outcome in our series showed multiple poor prognosis factors upon initial admission to our hospital. Each had had delayed diagnoses with initial skin rash at admission (30 and 14 days); one case even received the culprit drug on the first day in the emergency room. Major visceral organ impairment (one with cirrhosis and the other with uremia) and in-take histories featuring multiple drugs were also noticed in both cases. Multiple complications — including gastrointestinal hemorrhage, electrolyte imbalance, and homodynamic shock were detected early within the first 3 days of hospitalization. Although intensive care was provided the conditions of the full-blown disease could not be reversed.

Although scientific improvements currently occur at a brisk pace, the actual mechanisms underpinning SJS and TEN are still unknown; hence, a widely accepted consensus therapy does not exist at present. Systemic steroids have been the main therapy for SJS and TEN in most dermatological centers — including ours — for years, in the belief that it suppresses the intensity of reaction and controls the extension of the necrolytic

### Table. 4 Clinical Parameter Associated with Hospitalization Duration

<table>
<thead>
<tr>
<th>Clinical parameter / case number</th>
<th>Hospital day, X ± SD, days</th>
<th>P value</th>
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<tr>
<td>Disease severity*</td>
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<tr>
<td>SJS n = 42</td>
<td>10.4 ± 6.4</td>
<td>0.002</td>
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<tr>
<td>TEN n = 8</td>
<td>21.5 ± 13.1</td>
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<tr>
<td>Treatment*</td>
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<tr>
<td>Systemic Steroid only n = 29</td>
<td>10.0 ± 6.4</td>
<td>0.012</td>
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<tr>
<td>Systemic Steroid + prophylactic antibiotics n = 10</td>
<td>18.4 ± 13.0</td>
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<tr>
<td>Supportive care n = 4</td>
<td>15.5 ± 5.7</td>
<td></td>
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<tr>
<td>Infection morbidity #</td>
<td></td>
<td>0.021</td>
</tr>
<tr>
<td>Yes n = 15</td>
<td>19.5 ± 11.9</td>
<td></td>
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<tr>
<td>No n = 15</td>
<td>10.9 ± 4.9</td>
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* Two expired patients of TEN are excluded
* 2 expired, 1 poor wound healing , 6 patients with initial infection presentation treated with empiric antibiotics are excluded
# Infection confirmation by culture reports
Abbreviation: X = mean, SD = standard deviation
process at an early stage. However, in our series, evidence supporting the use of steroid therapy was not sufficient, due to the lack of prospective, randomized-control study.

Regarding the issue of steroid therapy, a great diversity is found in the literature. The 67 cases in Patterson’s series routinely received intravenous methylprednisolone (160-240 mg per day) and none showed any mortality or morbidity. However, some studies have claimed the effects of steroid therapy. Increasing mortality and morbidity was found in TEN patients receiving systemic steroid, even in burn care center. Decreased incidences of Candida sepsis and ulceration of gastrointestinal columnar epithelium were found in supportive care patients, compared to those partaking in steroid therapy. In our series, the mean hospital time of steroid therapy patients was actually shorter than those of other therapy groups. But infection was obviously higher in this group and sepsis was noted only in the systemic steroid group. Based on our results, there may be some benefit to steroid use in early stages, to prevent inflammation and further disease progression; the risk of infection morbidity should nonetheless be considered. Overall, the benefits of steroid therapy are still being debated.

Fever is a commonly reported prodromal symptom, with variations among SJS patients and in almost 100% of TEN patients. Fever can be highest up to 40°C in drug hypersensitivity syndrome but it usually subsides within a few days (most reports: one to three days). This observation is also similar to most of the cases in our series. We noticed only one case with prolonged high fever after admission and no further skin necrolysis extension; infection was finally confirmed. It is believed that fever is caused by drug themselves or a release of some pyogens from the necrotic epidermis rather than by the infection and so prophylactic antibiotics are generally not recommended in the literature. However, the experience of Peter et al. counters this opinion, and they suggest that prophylactic antibiotics may decrease the mortality rate by lowering the infectious threat to SJS and TEN patients. In our series, penicillin or first-generation cephalosporin was usually the first choice for prophylactic use due to the defective skin barrier in SJS-TEN patients; they may also take the risk of cross-reactions with possible offending drugs. Additionally, the indwelling of more catheters for administration of antibiotics also predisposes a patient to sepsis. Our patients received both types of prophylactic antibiotics, and the steroid group showed a worse clinical outcome. In our series, the prophylactic prescription offered no benefit to decrease hospitalization time, but bias arising from difference in condition severity and in therapy administration can’t be completely avoided. A more toxic presentation and severe skin detachments would likely prompt our doctors to administer advanced and defensive medical therapy, for example. In our opinion, closely following clinical changes—such as evaluation of prolonged fever without further skin lesions, sudden body temperature change, and wound discharge condition would provide more valuable clues than prodromal fever alone, in decision-making antibiotics prescription.

In terms of causative drugs in the SJS/TEN spectrum in Taiwan, carbamazepine was the most commonly administered drug in our population, followed by antibiotics and allopurinol according to previous retrospective reports of National Taiwan University Hospital in 1996 and 2005. In our study, change of position for carbamazepine, but our series showed higher incidences of NSAID, allopurinol, and antibiotics. As we know, first-line empiric antibiotic therapy is now the cephalosporin group and sulfonamide is no longer popular; this may explain our observation. Scientific and genetic evi-
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dence for carbamazepine association with eruption in the Chinese population was also provided by Chung et al. at the Taipei Chang Gung Memorial Hospital. As shown in Table 3, the most common underlying systemic diseases justifying drug use were pain-related disorders. The main indication of carbamazepine prescription in our reports is also for pain-control rather than seizure treatment; it is not only the increasing use of carbamazepine, but also its high sensitivity that creates high incidence of severe drug eruption in our population. In contrast to Halevy’s series, the most commonly prescribed medication—allopurinol had relatively lower incidence in Taiwan. To the best of our knowledge, however, allopurinol is also widely prescribed in general practice in Taiwan. The genetic diversity among different races is considered a reasonable explanation for variations in drug administration and patient reactions therein. Hence, endemic data of offending drugs should be captured.

The histopathological classification of SJS and TEN is difficult due to a lack of clear-cut criteria, differently evolved skin lesions, and different biopsy times before or after steroid therapy. (In any case, skin biopsies are not regularly performed at our facility). Rzany et al. provided a large series with 111 slides showing that both the necrotic keratinocytes and the vacuolar epidermal junction are, in all cases, independent of severity of disease. Mononuclear cells mainly appear perivascular infiltration and present as scant inflammation over the epidermis and dermis; these characteristics were especially mentioned in the difference between SJS-TEN and erythema multiforme, as cited in Fitzpatrick textbook. These characteristics are similar to ours but a difference in density of infiltration was not found. The choice of biopsy lesion type and timing are considered major factors that influence pathology findings; in fact, they are the reasons why pathological results cannot provide us with definitive diagnosis for these diseases. According to our results, steroid treatment may play a role in shortening hospitalization duration, as some slides presented with dense inflammation. To our surprise, in our cases, eosinophils were not common; in fact, they were rarely found despite the fact they were have traditionally been pathological point for drug eruption. Highly prevalent steroid treatment upon admission was thought to be possible factor decreasing the eosinophils infiltration. However, there is no data in the literature proving the relationship between steroid use and eosinophils infiltration.

Visceral organ involvement was not uncommon with previous reported 8.1%–61.5% in SJS and 53.8% in TEN. Liver function abnormality was noted in about half the patients and decompensate liver function was noted in one of our mortality cases with primitive liver cirrhosis. Drug-mediated hepatitis is an idiosyncratic toxicity wherein unusual drug metabolites and immune-mediated hepatocyte injury are the main pathogenetic mechanisms. Abnormality of liver function did not correlate with disease severity or hospitalization duration in our observation. It’s reasonable to say that the transaminase level could have been influenced by many factors such as inflammatory reaction, fatty liver and underlying virus hepatitis status. This observation is compatible with the previous documented severe illness score system (SCORTEN), wherein liver function was found not to be a good predictor of disease severity in cases of SJS-TEN.

In addition to acute infectious morbidity, which mostly causes fatal outcomes; the late sequela of ocular mucosa scarring affects quality of life after discharge. It can be highest among TEN patients up to 30%. Routine ophthalmic consultation with lubrication, steroids, and antibiotic eye drops is well established in our department. Although the most
severe form of sequela-based blindness has not been found, corneal scarring can not be completely eliminated. Early diagnosis and intervention should be afforded to this condition. Only a few cases (8/52, 15%) in our series required further ophthalmic follow-up after discharge.

This is an observational retrospective study with many limitations, especially in terms of evaluating therapeutic effect. First, treatment selection does not depend only on disease severity; even severe cases may have had only supportive care, due to steroid side effects. Second, the baseline of patient condition is so complex in our study that it is difficult to estimate the objective treatment effect. Hospitalization duration, as calculated in our study, is not representative of all treatment outcomes. Furthermore, each therapy group comprises a relatively small sample size. In this study, we discussed the clinical and treatment experiences related to potentially fatal and high-morbidity diseases.

In conclusion, prevention and early detection is critical to solve this disease. Differences in disease severity and infectious morbidity mainly influenced the course of hospitalization in our series. Endemic common offending drugs in our study—carbamazepine, NSAID and allopurinol—should all be considered by physicians. Most patients in our series had good clinical outcomes in the general ward care facility; the intensive burn center care was selectively provided for severe or complicated cases. Based on our results, infection morbidity is still a major concern in mitigating a patients’ disease course. In our opinion, a close monitoring of infectious signs and symptoms, especially in patients who received steroid therapy, should be emphasized, as it provides more valuable clues than routine prophylactic antibiotics. According to our observations, early administration of systemic steroids may be beneficial in terms of inflammation prevention and disease progression. Short-term use to preclude infection morbidity, as well as a tapering dose as soon as possible, is suggested.

REFERENCES
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史帝文強生症候群及毒性表皮溶解症：
南台灣病人流行病學回溯性研究

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高雄長庚紀念醫院皮膚科¹ 朱冠州皮膚科診所²

背景：史蒂文強生症候群及毒性表皮溶解症是嚴重且致命性的藥物不良反應。目前對最合適的治療方式仍有爭議。在台灣此類疾病的流行病學資料仍然有限。
目的：評估全身類固醇療法對史蒂文強生症候群及毒性表皮溶解症的療效，進一步也重新統計該疾病相關的流行病學資料。
方法：本研究回溯性地收集本院過去五年內符合診斷的住院病例，評估分析全身性類固醇的治療效果，此外也統計所有病例的死亡率、併發症以及最常見的致病藥物種類。
結果：一共蒐集了52個病例；其中10位分類為毒性表皮溶解症、其它42位為史蒂文強生症候群。整體的死亡率為3.8%，住院中相關的感染併發症為23%。在常見引發的藥物方面，抗癲癇藥物（特別是carbamazepine）為最常見，依次為非類固醇止痛藥、降尿酸藥及抗生素。研究中顯示早期類固醇投與治療的確較支持性療法可以縮短住院天數（p= 0.012）。
結論：治療上早期類固醇投與治療的確有幫助，特別是減少發炎及減緩疾病進展方面，而感染的併發症在投予類固醇治療的病人中格外需要注意。（中華皮誌：27: 15-26, 2009）