Original Article

A Systematic Review of Stevens-Johnson Syndrome and/or Toxic Epidermal Necrolysis over a Period of 20 Years in Thailand

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Objective: To perform a systematic review of published literature to generate a large-scale database in order to report the causes, treatment, and clinical outcomes of Stevens-Johnson syndrome [SJS] and/or toxic epidermal necrolysis [TEN] in Thailand.

Materials and Methods: Articles from 1995 to 2014 describing SJS and/or TEN in Thai population were searched in PubMed, MEDLINE, EMBASE and Thai Index Medicus electronic databases. Data were analyzed for the causes, management, and clinical outcomes of SJS and/or TEN in Thailand.

Results: From 87 references, 9 references were included for the final analysis. Five hundred and forty cases of SJS and/or TEN were reported: 326 (60.4%) of whom were adults and the remaining 214 cases (39.6%) were children. The most common cause of SJS and/ or TEN in both adults (100%) and children (97.2%) was drug. The second most common cause of SJS and/ or TEN in children (2.8%) was Mycoplasma infection. The major culprit drugs in adults were cotrimoxazole (22%), nevirapine (8.6%) and allopurinol (8.3%), and in children were penicillin (21.1%), phenobarbital (16.3%) and carbamazepine (13.5%). In adults, the most common complication was hepatitis (12%) while the most common complication in children was skin infection (8.4%). The death rate from SJS and/or TEN in adults was 11.3%, which was significantly higher than the 6.1% rate in children ($p = 0.04$). Intravenous corticosteroids treatment in SJS and/ or TEN among children was significant higher than adults (59.2% vs. 27.0%, $p<0.01$).

Conclusion: The major cause of SJS and TEN among Thai adults and children was drug reaction. Antibiotics were the most common culprit drug group in both adults and children. The mortality rate in SJS and/or TEN among adults was significant higher than that in children.

Keywords: Stevens-Johnson syndrome, Thailand, Toxic epidermal necrolysis

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Stevens-Johnson syndrome [SJS] and/or toxic epidermal necrolysis [TEN] are uncommon dermatological conditions characterized by acute keratinocyte necrosis[1,2]. The yearly rate of hospitalized patients with SJS and/or TEN is 6.1 to 7.4 cases for each million in the US[3,4]. In Germany, the annual incidence rate of hospitalized patients with SJS and TEN is 1.1 and 0.9 cases for every million, respectively[5]. Compared to adults, the annual incidence rate among children is substantially higher, with a reported rate of 35.5 cases per million[4]. These dermatological conditions are considered lethal medical emergencies, which are divided into three groups: SJS, SJS-TEN overlap and TEN involve <10%, 10 to 30% and >30% of the body surface area, respectively[6]. The gold standard for the diagnosis of SJS and TEN is based on clinical symptoms and signs together with histological features of skin biopsy[2].

Several factors have been reported to be implicated in the etiology of SJS and/or TEN.

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Medications are the most common identified factors, causing 77 to 95% of SJS and TEN. More than 100 medications have been acknowledged[7]; however, the common causative drugs are antibiotics, anticonvulsants, and nonsteroidal anti-inflammatory drugs. Aside from medications, Mycoplasma and herpes simplex virus are well-recognized as the causes of SJS and/or TEN without initial exposure to drugs[2]. An important issue in the treatment of SJS and/or TEN is that it requires rapid diagnosis, identification and withdrawal of the causative drug inducing the inflammatory reaction, assessment of the severity and prognosis using SCORTEN, implementation of treatment and transfer of patients to specialized centers, which have been shown to lower complications and mortality[2,8]. Treatment modalities include intensive supportive management, systemic corticosteroids and intravenous immunoglobulin. Nevertheless, the utilization of specific therapies remains controversial[9].

Because SJS and/or TEN are uncommon dermatologic diseases, there has been no large-sample study in Thailand. The main objective of this review is to conduct a systemic review of published literature to generate a large-scale database with a specific end goal to exhibit the causes, treatment, and clinical outcomes of SJS and/or TEN among Thai population.

Materials and Methods

The search was focused on publications describing or potentially describing SJS and/or TEN in Thailand. The electronic search strategy included the following key terms: 'SJS' or 'TEN' and 'Thai' or 'Thailand'. The comprehensive online search included the electronic databases-PubMed, MEDLINE, EMBASE and Thai Index Medicus. Article published from 1995 to 2014 were included. Articles in English and Thai language were considered. Two reviewers selected articles independently by the search from October 2014 to April 2015. The retrieved reference was assessed for possible inclusion based on the evaluation of the title and the abstract, or in full article if no abstract was available. Review articles, letter of the editor, editorials and commentaries were excluded. Protocol of this study was registered in the PROSPERO register for the systematic review (Center for reviews and dissemination [CRD] 42014013133).

Inclusion criteria

- Studies were conducted in Thailand.
- Retrospective studies and case series of SJS and/or TEN.
- All age groups and with established diagnosis of SJS and/or TEN by clinical criteria.

Exclusion criteria

- Studies were not conducted in Thailand.
- Studies were not specifically describing the cause of disease.

Review methods

The 'STROBE statement'- a reporting guideline with checklists for the observational studies that are considered essential for good reporting was used to assess the quality of the included studies. For each study, information was collected for SJS and/or TEN. Selected studies were divided into two categories (adults and children). Data collected were demographic, type of clinical settings, co-morbid conditions, causes of disease, use of corticosteroid and intravenous immunoglobulin, duration of hospital stay, complications, and mortality.

Outcome analysis

Data for primary outcome variable were extracted from the studies and summarized using absolute numbers of cases and percentage. Chi-square test was used to compare the proportion of causative drugs. Data for secondary outcome variables were extracted and summarized using ranges, means or medians as provided by the authors. SPSS software version 17.0 was used for statistical analysis. The $p<0.05$ was considered significant.

Results

Literature search

The literature search yielded 87 references, 75of which were excluded as per criteria. Twelve references were fully evaluated, and 9 were included as per criteria for the final analysis[10-18].

Characteristic and quality of the studies included

All nine studies were retrospective studies. Six studies were conducted in adults and three studies were conducted in children. All hospitals were tertiary hospitals. Four studies were from Bangkok (Capital city) and five studies were from other provinces (Table 1). Two studies followed Naranjo's algorithm[13,17].

Characteristics of the patients

A total of 540 cases of SJS and/or TEN were reported. The incidence rates were 9 cases per year in adults and 5 cases per year in children. Of the 540 cases

included, 326 cases (60.4%) were adults and 214 (39.6%) were children. The mean ages of adults and children were 42 years and 5.4 years, respectively. Most of them were male. The most common co-morbidity of adult patients was HIV infection (52.1%). No underlying disease was reported in children.

The percentages of adult patients who encountered SJS, TEN and SJS-TEN overlap were 84.7%, 12.9% and 2.4%, respectively. The percentages of children who were diagnosed with SJS was 97.2% and with TEN was 2.8%. Drug reaction was the most common cause of SJS and/or TEN in both adults (100%) and children (97.2%). Mycoplasma infection was the second most common cause of diseases in children, with a reported rate of 2.8% (Table 2).

Incubation period and clinical features

Duration between drug intake and the onset of symptoms ranged from 1 to 14 days in both children and adults. The median of incubation period was 7

Table 1. Characteristics of the included studies

Studies	Patients (n)	Hospital	Province	Patient group based on age
Thanajantaporn et al	106	Bamrasnaradura Institute	Nonthaburi	Adult
Roongpisuthipong et al	87	Vajira Hospital	Bangkok	Adult
Sukkul et al	56	Chulalongkorn Hospital	Bangkok	Adult
Limpawattana et al	45	Srinagarind Hospital	Khon Kaen	Adult
Thammakumpee et al	25	Chonburi Hospital	Chonburi	Adult
Limtanyakul et al	8	HRH Princess Maha Chakri Sirindhorn Medical Center	Nakhon Nayok	Adult
Singalavanija et al	189	Queen Sirikit National Institute of Child Health	Bangkok	Children
Reakatanan et al	17	Ramathibodi Hospital	Bangkok	Children
Leksoontorn K.	8	Maharat Nakhon Ratchasima hospital	Nakhon Ratchasima	Children

Table 2. Demographics of Stevens-Johnson syndrome and/or toxic epidermal necrolysis cases in adult and children group (n = 540)

	Adults (n = 326), n (%)	Children (n = 214), n (%)	*p*-value
Mean age (years)	42.0±16.7	5.4±3.6	<0.01
Male	177 (54.3)	133 (62.1)	0.07
Underlying disease			
Cardiovascular disease	33 (10.1)	0 (0)	<0.01
HIV infection	170 (52.1)	0 (0)	<0.01
Malignancy	12 (3.7)	0 (0)	<0.01
Diagnosis			
SJS	276 (84.7)	208 (97.2)	<0.01
SJS-TEN overlap	8 (2.4)	0 (0)	0.02
TEN	42 (12.9)	6 (2.8)	<0.01
Cause of disease			
Drug-related	326 (100)	208 (97.2)	<0.01
Mycoplasma infection	0 (0)	6 (2.8)	<0.01
Intravenous steroid use	88 (27.0)	122 (59.2)	<0.01
Intravenous immunoglobulin	0 (0)	1 (0.5)	0.02
Mean length of stay (day)	13.6±9.7	5.5±2.2	<0.01

SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis

days in adults and 2 days in children[13,17]. Prominent prodromal features were fever (93%), headache (70.8%) and myalgia (60.9%)[10]. Most of lesions were maculopapular rash (64.7%), followed by target lesions (29.4%) and bullae lesions (9.1%)[17]. Associated symptoms were itching (52.9%) and burning sensation (18.9%)[10]. Mucosal involvements were pooled from two studies. In adults, ocular, oral and genital mucosa involvements were involved in 74%, 68.9% and 31.1%, respectively[10,11]. The mucous membrane involvements in children were eye, mouth and genitalia, which occurred in 70.6%, 100% and 35.3%, respectively[17].

Culprit drugs

Drugs were identified to be the most common cause of SJS and/or TEN in both adults (100%) and children (97.2%). Among 326 adults, there were 360 SJS and/or TEN events occurring after prescribing medications (average of 1.1 drugs per case). Regarding the culprit drugs in children, there was an average of one drug per case.

Antibiotics were the most common causative drug group in adults and children. In adults, the three major culprit drugs are cotrimoxazole (22%), nevirapine (8.6%) and allopurinol (8.3%). In children, the three major culprit drugs are penicillin (21.1%), phenobarbital (16.3%) and carbamazepine (13.5%). Details regarding culprit drugs and rates of SJS and/or TEN in both adult and child populations are summarized in Table 3.

SCORTEN, complications and mortality

Data were pooled from two studies to calculate the mean SCORTEN and the percentage of mortality according to SCORTEN at the time of admission[11,15]. The mean of SCORTEN on the day of admission was 1.9 in adults. The observed mortality rates were correlated with the predicted mortality rates, except for the SCORTEN scores of 4 and ≥5 (Table 4).

The most common complications found in adults was hepatitis (12%) and in children was skin infection (8.4%). Adults had higher percentages of complications which included pneumonia, hepatitis,

Table 3. Comparison of incidences of culprit drugs in Stevens-Johnson syndrome and/or toxic epidermal necrolysis cases between adult and children group

Culprit drugs	Adults (n = 360), n (%)	Children (n = 208), n (%)	*p*-value
Antibiotics	136 (37.8)	77 (37.0)	0.86
Penicillin	20 (5.5)	44 (21.1)	<0.01
Cotrimoxazole	81 (22.5)	20 (9.6)	<0.01
Cephalosporin	9 (2.5)	8 (3.9)	0.36
Carbapenem	2 (0.6)	0 (0)	0.28
Macrolide	2 (0.6)	4 (1.9)	0.12
Quinolone	17 (4.7)	0 (0)	<0.01
Doxycycline/tetracycline	3 (0.8)	1 (0.5)	0.63
Clindamycin	2 (0.6)	0 (0)	0.28
Anticonvulsants	40 (11.1)	70 (33.7)	<0.01
Phenytoin	25 (6.9)	8 (3.9)	0.13
Carbamazepine	12 (3.3)	28 (13.5)	<0.01
Phenobarbital	1 (0.3)	34 (16.3)	<0.01
Lamotrigine	2 (0.6)	0 (0)	0.28
NNRTIs	36 (10.0)	0 (0)	<0.01
Nevirapine	31 (8.6)	0 (0)	<0.01
Efavirenz	5 (1.4)	0 (0)	0.09
Allopurinol	30 (8.3)	0 (0)	<0.01
Fluconazole	23 (6.4)	0 (0)	<0.01
Anti-tuberculosis*	21 (5.8)	0 (0)	<0.01
NSAIDs	12 (3.3)	8 (3.9)	0.75
Other drugs	62 (17.3)	53 (25.4)	0.02

* Anti-tuberculosis (isoniazid, rifampicin, pyrazinamide, and ethambutol)
NNRTIs = non-nucleoside reverse transcriptase inhibitors; NSAIDs = nonsteroidal anti-inflammatory drugs

acute kidney injury and sepsis compared to children (p<0.01). The mortality rates were 11.3% in adults and 6.1% in children, which was statistically significant different (p = 0.04) (Table 5). In adults, mortality rates were 8.3% in SJS, 50% in SJS-TEN overlap and 33.3% in TEN. In children, mortality rates were 4.8% in SJS and 50% in TEN. The causes of death were multiple organ failure, septicemia and acute respiratory distress syndrome[12,13].

Duration of hospital stay and management

The mean length of stay in adults was 13.6 days, which was significantly longer than an average of 5.5 days observed in children (p<0.01). The rate of intravenous corticosteroid therapy in children was significantly higher than that in adults (59.2% vs. 27.0%, p<0.01). Only one study reported that the use of intravenous corticosteroids might yield benefit[11]. The form of corticosteroid used was parenteral dexamethasone with an average dosage of 13.7 mg/day (8 to 16 mg/day) or equivalent steroids. The mean duration of corticosteroid therapy was 5.6 days (2 to 15 days)[11]. One child with TEN received intravenous immunoglobulin for 5 days after no improvement with corticosteroid therapy[17].

Discussion

In this study, the clinical characteristics of SJS and/or TEN among Thai population were

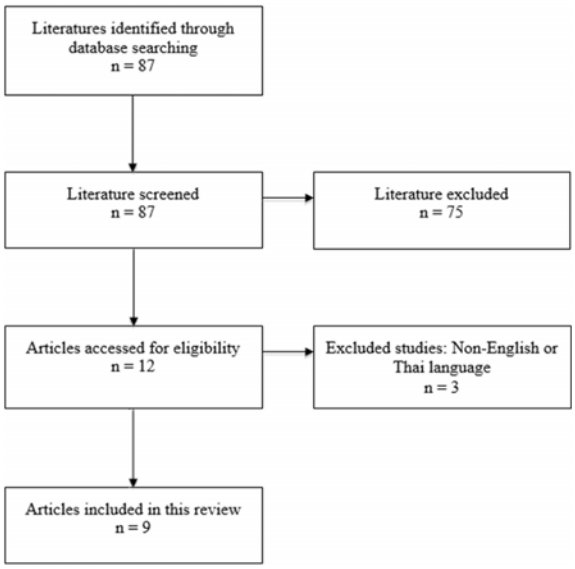

Figure 1. Flow diagram: data collection and selection of studies.

Table 4. Comparison between observed and predicted mortality by SCORTEN in adult patients (n = 95)

SCORTEN at admission	Total number of cases	Observed mortality (%)	Predicted mortality (%) (95% CI)
≤1	33	12.1	3.1 (0.1 to 16.7)
2	38	18.4	12.1 (5.4 to 22.5)
3	16	25.0	35.3 (19.8 to 53.3)
4	5	80	58.3 (36.6 to 77.9)
≥5	3	33.5	>90 (55.5 to 99.8)

CI = confidence interval

Table 5. Comparison of complications and mortality in Stevens-Johnson syndrome and/or toxic epidermal necrolysis cases between adult and children

	Adults (n = 326), n (%)	Children (n = 214), n (%)	p-value
Corneal abrasion	1 (0.3)	4 (1.9)	0.06
Skin infection	22 (6.7)	18 (8.4)	0.47
Pneumonia	20 (6.1)	1 (0.5)	<0.01
Hepatitis	39 (12.0)	11 (5.1)	<0.01
Acute kidney injury	19 (5.8)	1 (0.5)	<0.01
Sepsis	21 (6.4)	2 (0.9)	<0.01
Death	37 (11.3)	13 (6.1)	0.04

systemically reviewed from the selected nine studies from 1995 to 2014. The mean age of Thai adult patients were 42 years, which was consistent with previous reports from Japan and China[19-21]. Among Thai children, the mean age at diagnosis were 5.4 years which was much younger than an average age of 11.9 years observed in Indian children[22]. Our results also showed that males were more likely than females to be affected by SJS and/or TEN in both adult and children populations. This finding was in agreement with other studies from West Germany and India[5,23].

Regarding underlying co-morbidity, one Thai population-based study reported that the incidence of SJS patients who were HIV positive was 0.7 cases per thousand per year[10]. This was compatible with the finding of one previous study which showed that the incidence of HIV infection among SJS and/or TEN patients was approximately 1 case per thousand per year[24], suggesting that the incidence in SJS and/or TEN was 1,000-fold higher than that in general population. With respect to mucous membrane involvement, the studies from Japan and Canada reported that conjunctiva was the most common mucosal lesion in SJS and/or TEN[25,26]. This study, which was conducted among Thai population, showed that conjunctiva involvement was the most common mucosal involvement only in Thai adults. Among Thai children, the most common mucosa lesion was mouth, whereas conjunctiva was the second most mucosa involvement.

Drug reaction was the most common cause of SJS and/or TEN in both adults and children. Mycoplasma infection was the second most common cause of diseases in children, while there was no case of mycoplasma infection in adults. *Mycoplasma pneumoniae* is the most common organism to cause SJS, especially in children and adolescence[27]. In Thai adults, the major culprit drugs were cotrimoxazole, nevirapine and allopurinol. These results were in line with one prior study from four countries in sub-Saharan Africa and the study from Kenya. The study from sub-Saharan Africa demonstrated that the most causative drugs were cotrimoxazole and nevirapine whereas the study from Kenya reported that cotrimoxazole and nevirapine were the most causative drugs[28,29]. Among Thai children, the major culprit drug groups were antibiotics, anticonvulsants and NSAIDs. The study from India revealed that the most common causative drug group in children was antibiotics, followed by NSAIDs and anticonvulsants[22].

In clinical practice, the use of intravenous corticosteroids in SJS and/or TEN is controversial. Corticosteroids has an immunomodulating effect through the inhibition of various cytokines. However, the use of corticosteroids may also increase of the risk of secondary infection and worsen healing. Due to the low incidence of diseases leading to difficulties in conducting randomized clinical trials, the use of corticosteroids as specific therapy for SJS and/or TEN have not reached evidence-based acceptance standards[30]. These reasons therefore limit the use of corticosteroids in real-life practice. In this study, the use of intravenous corticosteroids in adults was 27% and in children was 59%. These rates were lower than those in the studies from Indonesia (100%) and Japan (67.8%)[25,31]. However, there was an upward trend towards increased use of corticosteroids among Thais as one study demonstrated that the rate of corticosteroid treatment has increased from 22% in 2003 to 2007 to 76% in 2008 to 2012[11]. One systematic review demonstrated that systemic corticosteroid therapy along with supportive treatment resulted in lower morbidity and mortality than supportive treatment alone among children with drug-induced SJS and TEN[32].

In the present study, the most common complication observed in Thai adults was hepatitis, which was consistent with previous studies from Japan, China and Indonesia[19,21,31]. The most common complication in children was skin infection, followed by hepatitis. The mortality rate of Thai adults was 11.3%, which was in the range of 10.1 to 15.6% in other studies from Asian countries[31,33,34]. With respect to child mortality, the rate in this study was 6.1%, which was lower than the rates of 9.5 to 10% in the studies from US and India[22,35].

Many limitations exist in the present study. First, the evidence in this systematic review was construct generally on observational literatures. So, there was no control group to ascertain the efficacy and safety of specific treatment in SJS and/or TEN. Second, the determination of SJS and/or TEN were conflicting among the included literatures. In this way, the misclassification of SJS and/or TEN was unavoidable. Third, the causative medications of SJS and/or TEN were identified by various methods. As only two studies followed the Naranjo's algorithm, the data of causative drugs might be incompletely collected. Finally, the important parameter like SCORTEN was available from only two studies. Therefore, the sample size was small. Future national and international registry system for SJS and TEN is necessary to fortify database

for further research about the causes, specific treatment and clinical results, e.g. outcomes of use of systemic corticosteroids and intravenous immunoglobulin.

Conclusion

The major cause of SJS and TEN among Thai adults and children was drug reaction. Antibiotics were the most common culprit drug group in both adults and children. The mortality rate in SJS and/or TEN among adults was significant higher than that in children.

What is already known on this topic?

From systematic review, the most common culprit drugs in SJS and/or TEN in both adults and children were antibiotics, anticonvulsants and NSAIDs, orderly[7,8]. The most common complications were hepatitis in adults and skin infection in children. In adults, the mortality rate was highest in SJS-TEN overlap cases while the mortality rate was highest in TEN cases among children patients[12,13].

What this study adds?

This study confirmed that antibiotics, anticonvulsants and NSAIDs were the most common culprit drugs in children. In Adults, the most common culprit drugs were antibiotics, anticonvulsants and NNRTIs, orderly. The incidence rates of allopurinol and NNRTIs as culprit drugs (8.3% and 10%, respectively) were higher than previous reviews in other populations.

Potential conflicts of interest

The authors declare no conflicts of interest.

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