

PROFILE AND TREATMENT OF STEVENS-JOHNSON SYNDROME PATIENTS IN DR. SOETOMO GENERAL HOSPITAL

Anggun Tera Rahmasari¹, Diah Mira Indramaya², Pudji Lestari³

¹Faculty of Medicine, Airlangga University

²Department of Dermatovenereology, Dr. Soetomo General Hospital

³Department of Public Health, Airlangga University

Corresponding author:

Anggun Tera Rahmasari

Faculty of Medicine, Airlangga University

Email: anggun.tera@yahoo.com

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Abstract

Background: Stevens-Johnson Syndrome (SJS) is a rare but potentially life-threatening form of Severe Cutaneous Adverse Reaction (SCAR). SJS is mostly caused by drugs and is associated with high morbidity and mortality. Moreover, no standard treatment has been established for SJS. The aim of this study is to present epidemiological features, etiologies, clinical outcomes, medical histories, and treatments of SJS patients at the Inpatient Units Kemuning I and II Dr. Soetomo General Hospital between 2011 until 2015.

Methods: This retrospective study used secondary data collected from medical records. All patients in the Inpatient Units Kemuning I and II of Dr. Soetomo General Hospital from the year 2011 until 2015 who was diagnosed SJS were included in this study.

Result: There were 29 medical records consisting of 23 females and 6 males with the diagnosis of SJS found in 2011-2015. Most patients were aged 25-44 years old, with no family history of SJS. A majority first presented with a clinical history of fever. The main cause of SJS in this cohort was amoxicillin. Mucosal areas that were involved the most was the eye and mouth. Systemic treatments for patients were corticosteroid. The average duration of treatment was 15,88 days. None of the patients died.

Conclusion: SJS was more common in females compared to males. The main systemic therapy in Inpatient Units Kemuning I dan II of Dr. Soetomo General Hospital was intravenous corticosteroid and no patients died.

INTRODUCTION

Stevens-Johnson Syndrome (SJS) is a rare Severe Cutaneous Adverse Reaction (SCAR) characterized by erythematous macules evolving to epidermal detachment and mucosa membrane erosions.¹ The involvement of at least two mucosal membranes are required for establishing the diagnosis of SJS.² In SJS there is less than 10% body surface area involved. Meanwhile, Toxic Epidermal Necrolysis (TEN) has the exact same clinical features with SJS, but with

involvement of more than 30% body surface area.³ Incidence of SJS was reported to vary from 1.2 to 6 per million patient per year and is a major concern due to its severe morbidity and mortality. Although the mechanism of SJS is still unclear, it is mostly associated with the use of certain drugs.

Other possible causes of SJS are infections, immunizations, environmental chemicals and radiation therapy. Drugs that commonly caused SJS include antibiotics, anti-convulsants, non-steroidal anti-inflammatory drugs (NSAIDs) and

allopurinol.⁴ Risk of SJS increases in patients with HIV, collagen vascular disease, and cancer.

Clinical symptoms vary among patients. The syndrome usually begins with the prodromal symptoms of fever, headache and myalgia.⁵ SJS lesions first appear erythematous then evolve into dusky or purpuric macules. The lesions usually have irregular shapes, discrete in the beginning then coalesce with one another.³ Early sites of cutaneous involvement are not limited to the trunk and the face, and often involve the palms and soles. More than 90% of patients have an involvement on the buccal, genital and or ocular mucosa. Some cases also involved the respiratory and gastrointestinal mucosa.⁶

Sepsis is the most common complication of SJS and the most common cause of patient death. Skin erosion leads to easier bacterial infection hence which leads to many complications. Genital erosions also can cause dyspareunia.^{2,6}

Score for Toxic Epidermal Necrolysis (SCORTEN) is a scale used for measuring level of severity from epidermal necrolysis. SCORTEN's function is for determining prognosis of SJS.^{3,6} History of the patient's disease, such as HIV, tuberculosis or diabetes also has an impact on prognosis, for example. If patient has history said diseases, then SCORTEN's score is 5 or more than 5.⁴

Table 1. SCORTEN

Parameter	Points
Age > 40 year	1
Blood Pressure >120/min	1
Cancer/Malignancy	1
>10% Body Surface Area	1
Serum Urea >10mm/L	1
Serum Bicarbonate <20mmL	1
Serum Glucose >14mm/L	1

Points	Mortality Rate
1	3,20%
2	12,10%
3	35,50%
4	58,30%
>5	90,00%

Adapted from Ho,2008

METHODS

This is a retrospective study which used secondary data collected from the medical records. Instruments used are medical records of patients

diagnosed with SJS in Inpatient Units Kemuning I and II Dr. Soetomo Regional Hospital in 2011-2015. Data obtained includes the age, gender, aetiology, medical history, inciting medications, clinical features, and family history. The treatment-regimens, length-of-stay, and mortality were also recorded.

RESULTS

The total number of patients that were hospitalized in Inpatient Units Kemuning I and II Dr. Soetomo General Hospital were 1750 during the study period of 2011-2015. Among these, 29 SJS cases were found. There were 5 (1,09%) cases in 2011, 4 cases in 2012 (0,95%), 5 cases in 2013 (1,1%), 4 cases in 2014 (1,5%), and 11 cases in 2015 5,5%). There were 22 (75,8%) females and 7 males (24,14%).

According to data from Inpatient Units Kemuning I and II from 2011-2015, the mean patient age was 36,58 years. Most patients diagnosed with SJS were in the 25-44 years old range with a total of 12 (41,37%) patients. The second most prevalent age group was 45-64 years old (34,48%) with a total of 10 patients, and third was 15-24 years old with a total of 7 patients (24,13%).

Patient history prior to SJS occurrence showed fever as the most common history which was present in 6 patients (20%), followed by epilepsy in 5 patients (16,67%). Other history of disease before the occurrence of SJS are Low Back Pain (3,33%), Systemic Lupus Erythematosus (3,33%), Common Cold (6,66%), Post Op Trepanation (3,33%), Headache (3,33%), Brain Tumor (3,33%), Post Op Kidney Stones (3,33%), Terminal Neuralgia (3,33%), and Convulsions (3,33%).

History of drug use in SJS patients revealed the most common eliciting drug as antibiotics followed by anti-epileptic medication (Table 2). However, since patients mostly consumed more than one drug, it is difficult to precisely determine which drug caused the SJS. Patients also had history of using herbal medicine.

The main systemic therapy given to patients were glucocorticoids, such as oral methylprednisolone 80-120 mg at 1.5-2 mg/kg/day or intravenous dexamethasone at 0.15-0.2 mg/kg/day. As much as 23 patients (79,31%) were treated with intravenous dexamethasone 3x2 mg/day, 2 patients (6,89%) were treated with intravenous

dexamethasone 2x4 mg/day, 2 patients (6,89%) were treated with oral dexamethasone 1.5-2mg/kg/day, and 2 patients (6,89%) were treated with oral methylprednisolone 80-120 mg. Patients also received antibiotic therapy. As much as 14 patients (48,27%) received intravenous gentamycin at 2x80 mg iv/day, 9 patients (31,03%) received cefotaxime 3x1 gram iv/day, 2 patients (6,89%) received ceftriaxone 2x1 gram iv/day, 3 patients (10,34%) received oral erythromycin 3x500 gram, and 1 patient (3,44%) received oral amoxicillin 3x500 gram.

Mucosal involvement in SJS patient occurred in buccal (20,68%), genital and eyes (3,44%), genital and buccal (10,34%), eyes and buccal (31,03%), and genital, buccal, and eyes (27,58%). The buccal area was the most common mucosal area involved in SJS.

Sepsis (3,44%), symblepharon (6,89%), and acute kidney injury (6,89%) occurred in patients as the complication of SJS. The average duration of stay was 15,68 days. From this study, we found no patients died because of SJS.

Table 2. History of drugs consumed before SJS occurrence by SJS inpatients at Units Kemuning I and II of Dr. Soetomo General Hospital.

No	History of Drug Use	Total (%)
1.	Antibiotic	25 (43)
	Sulfamethoxazole	1 (1,75)
	Tiamphenicol	3 (5,26)
	Cefadroxil	5 (8,77)
	Amoxicilin	6 (10,52)
	Levofloxacin	3 (5,26)
	Ceftriaxone	2 (3,50)
	Ciprofloxacin	2 (3,50)
	Cefixime	3 (5,26)
2.	Anti-epileptics	10 (17,54)
	Carbamazepine	5 (8,77)
	Phenytoin	4 (7,01)
	Valproic Acid	1 (1,75)
3.	Analgesic	17 (31,48)
	Paracetamol	13 (22,80)
	Salicylic Acid	1 (1,75)
	Piracetam	1 (1,75)
	Tinoridine	1 (1,75)
	Mefenamic acid	2 (3,50)
4.	Antidepressants	1 (1,75)
	Amitriptyline	1 (1,75)
5.	Allopurinol	3 (5,26)
6.	Acyclovir	1 (1,75)
7.	Jamu (herbal medicine)	3 (10,52)
Total		57 (100)

*) Patients can use >1 drug

Source: Secondary Data

DISCUSSION

The 5-year incidence of SJS in Inpatient Units Kemuning I and II is 1,65%. This is similar to the incidence range in RSUD Dr. Moewardi Surakarta from August 2011–2013, at 2,93%–3,30%. The most common age range in SJS patient is 25-44 year. The average in patients' age is 36,58 year with standard deviation 14,23.¹¹ The number of females diagnosed was greater than males. This is in line with the study by Allamore and Roujeau which found that females have higher risk of SJS.²

According to Clinical Practice Guidelines SMF Dermatovenerology of Dr. Soetomo Regional Hospital,⁷ management of SJS need to be performed in specialized rooms. However due to room limitations, patients were not transferred to the room. According to studies by Kim et al and Yim et al, SJS patients who are treated in burn intensive care units showed faster reepithelization time of the SJS skin lesion.^{8,9} Stopping the medication that caused SJS is also an important thing that impacts treatments success,³ as morbidity and mortality will increase when drug discontinuation is delayed.¹⁰

Correction of fluid balance, electrolyte, and protein was performed in all patients. Patient treatment also included control of the body temperature and provision of adequate nutrition. Patients were mainly treated with corticosteroids. The use of corticosteroid depends on country use. Germany also uses corticosteroid as the main therapy, while in France, corticosteroid is used as the main therapy only in a quarter of patients. The maximum corticosteroid dosage allowed is 250 mg in Germany and 75 mg in France. Level of treatment success by using corticosteroid in Germany is 59% and in France is 27% .¹ In a study from Tan and Tay⁴ corticosteroid was used in 16 out of 18 SJS patients. No patients experienced complications. The study stated that corticosteroid use is better given before tissue damage or further phases.⁴

According to that study, antibiotics were used if indications were clear.⁴ But in this study, we found that antibiotics were used because no patients were treated in a special room. It increases the risk of infection in the patient if they were not given antibiotics. All patients were given high-calorie and high-protein nutrition during their stay.

Patients with a history of epilepsy have a high incidence of SJS because due to the consumption of anti-epileptics, which has been highly associated with risk of SJS. Anti-epileptic drugs with the high SJS risk include carbamazepine, phenobarbital, and phenytoin.² From the five epilepsy patients, three patients consumed carbamazepine, and one patient consumed phenytoin.

According to Allanore and Roujeau,² other drugs with high SJS risk include allopurinol, sulfamethoxazole, sulfadiazine, sulphapyridine, sulfadoxine, sulfasalazine, carbamazepine, lamotrigine, phenobarbital, phenytoin, phenylbutazone, nevirapine, oxicam Nonsteroidal Anti-Inflammatory Drug (NSAID), and thioacetazone. Drugs with low risk for causing SJS are diclofenac, aminopenicillin, cephalosporin, quinolones, cyclin, and macrolide. Three patients consumed *jamu* herbal medicine before the occurrence of SJS. *Jamu* is a concoction of herbs such as roots, leaves, etc. Indonesians prefer consuming *jamu* to reduce pain. According to a study on 10 *jamu* herbal medicine samples performed in Surakarta,¹² two contained diclofenac sodium and two contained phenylbutazone. So, it does not rule out the possibility that SJS patients who consumed herbs also consumed sodium diclofenac, phenylbutazone or other drugs in the category.

There was no family history of SJS in this cohort of patients, and there were no racial or ethnic connections between drugs which trigger SJS reaction. Previous studies have shown associations between HLA-B*15:02 and carbamazepine-induced SJS in the Han Chinese, Thailand, Indian, and Malaysian population. Relationship between HLA B*58:01 with allopurinol-induced SJS is also present in the European, Japanese, Han Chinese, and Thai populations. This has been the basis of recommendations for physicians to be more cautious when prescribing certain drugs to some ethnicities.⁴

The average length of stay was 15,68 days with a standard deviation of 5,84. The longest period of hospitalization was 26 days and the shortest duration of hospitalization was 4 days. The patient discharged in the fourth day did so due to his parents' wishes. Two patients were discharged after 26 days in hospital because they had a bad

condition. One of them has the increased serum transaminase until 491 U/dl.

There were no patients who died in this cohort. A study from Mockenhaupt¹³ in Germany showed that SJS mortality ranges from 5% until 12%. The study from Tan and Tay⁴ also showed there were no patients who died because of SJS In August 2011– August 2013, there were no patients that died because of SJS in RSUD Dr. Moewardi Surakarta.¹¹

CONCLUSION

Early diagnosis and identification of medications that cause SJS is very important. Early discontinuation of the eliciting drug and provision of the correct treatment is key for mortality reduction. In this study there were 29 SJS cases which were mostly elicited by medications. No patients in this cohort died, and the main therapy used was corticosteroid.

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