A Four Years Retrospective Study of Stevens Johnson Syndrome: Toxic Epidermal Necrolysis Treatments in a National Tertiary Referral Hospital

Sarah Mahri, Teffy Nuary, Fadhli A. Mughni, and Windy Keumala B.
Department of Dermatology and Venereology, Faculty of Medicine Universitas Indonesia / Dr. Cipto Mangunkusumo National General Hospital, Jakarta

Keywords: Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Treatments

Abstract: Stevens-Johnson syndrome (SJS) and/or toxic epidermal necrolysis (TEN) are drug reactions associated to high morbidity and mortality. Prompt diagnosis and management may reduce the mortality rate. The research aims to evaluate the consistency of current treatments for SJS/TEN with the clinical pathway by Dr. Cipto Mangunkusumo National General Hospital and Indonesian Society of Dermatology And Venereology (ISDV). A retrospective review was conducted on patients with SJS/TEN admitted to Dr. Cipto Mangunkusumo National General Hospital, Jakarta during January 2014 to December 2017. The data were collected from paper-based and electronic health medical record database. A total of 34 cases of SJS/TEN were admitted, but only 30 cases with complete data was included, comprising of 20 males and 10 females with the mean age were 37.5 (15-70) years. Carbamazepin was the most common culprit drug. All patients were treated with intravenous methylprednisolone. The average length of stay were 6 days (3-20) in SJS, 8 (3-18) in SJS-TEN, and 11 (4-18) in TEN, while the mortality rate were 18.2% in SJS, 8.3% in SJS-TEN, and 14.3% in TEN. As conclusion, corticosteroids may contribute to reduced mortality rate in SJS/TEN without increasing secondary infection and serious sequele. The current treatments for SJS/TEN in our hospital is consistent with the clinical pathway by Dr. Cipto Mangunkusumo National General Hospital and Indonesian Society of Dermatology And Venereology (ISDV). Further well-designed studies are required to compare the effect of corticosteroids treatment for SJS/TEN to other medications.

1 INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening diseases characterized by widespread red rash, blisters, and shedding of dead skin, with mucosal involvement. The incidence of SJS/TEN has been reported to be 1.5–1.8/per million persons per year. SJS and TEN, based on clinical manifestations, are generally considered as different spectrum of the disease. Bastuji-Garin et al. proposed that disease classification should be based on the percentage of the total body surface area (BSA) of the epidermolysis or epidermal detachment. Epidermal detachment <10% of the BSA is classed as SJS, detachment above 30% as TEN, and detachment between 10% and 30% as intermediate (SJS/TEN overlap). SJS/TEN usually caused by medications (Wang & Mei, 2017; Bastuji et al., 1993).

In addition to the damage to the skin, gastrointestinal tract, and respiratory tract mucosa, SJS/TEN can also associated with visceral involvement (e.g liver, kidneys, lungs, and hematopoietic system), leading to organ dysfunction or even failure. The mortality rates of SJS and TEN are 10% and 34%, respectively (Kim et al., 2012; Lee et al., 2011).

SCORTEN, a severity-of illness scoring system for TEN was used to evaluate prognosis. The SCORTEN criteria are: serum blood urea nitrogen >10 mmol/L, serum bicarbonate <20 mmol/L, serum glucose >14 mmol/L, age >40 years, malignancy present, heart rate >120 bpm, and percentage of BSA with epidermal detachment >10%. The mortality rate was predicted according to the SCORTEN total score as follow: 1 point, 3.2%; 2 points, 12.1%; 3 points, 35.3%; 4 points, 58.3%; and 5 or more points, 90% (Fouchard et al., 2000).

Mahri, S., Nuary, T., Mughni, F. and B., W.
A Four Years Retrospective Study of Stevens Johnson Syndrome: Toxic Epidermal Necrolysis Treatments in a National Tertiary Referral Hospital.
DOI: 10.5220/0008151300830087
In *Proceedings of the 23rd Regional Conference of Dermatology (RCD 2018)*, pages 83-87
ISBN: 978-989-758-494-7

The treatment for these diseases is not well established all over the world. Clinical pathway 2017 for SJS/TEN treatments by Indonesian Society of Dermatology And Venereology (ISDV) include discontinue potential offending drugs, hospitalization, ophthalmologist consultation, systemic corticosteroids: intravenous dexamethasone prednisone equivalent dose 1-4 mg/kg/day for SJS, 3-4 mg/kg/day for SJS-TEN, and 4-6 mg/kg/day intravenous; IVIG high dose 1 g/kg/day for 3 days in TEN; cyclosporine; and combination IVIG and systemic corticosteroids, and topical treatment include petrolatum gel with parafin liquid or debridement. In addition to clinical pathway by ISDV, clinical pathway by Dr. Cipto Mangunkusumo National General Hospital for the treatment of SJS/TEN include identify and discontinue potential offending medications/drugs and other drugs that can cross react, hospitalization, intravenous fluid drug, systemic corticosteroids: intravenous methylprednisolone (prednisone equivalent dose) 1-2 mg/kg/day for SJS; 2-3 mg/kg/day for SJS-TEN; and 3-4 mg/kg/day for TEN, topical treatment for erosion with 1% salicylic acid in cream or vaselin album or fucidic acid cream 2%, Nacl 0.9% for crusts lesions, and consultations to ophthalmologist; dentists, internist; and otolaryngologist.

We conducted a retrospective review on patients admitted to Dr. Cipto Mangunkusumo National General Hospital, Jakarta with a diagnosis of SJS, SJS-TEN overlap and TEN based on clinical features during four years. The aim of this study is to evaluate the consistency of SJS/TEN current treatments with the clinical pathway by Dr. Cipto Mangunkusumo National General Hospital and Indonesian Society of Dermatology And Venereology (ISDV).

2 METHODS

A retrospective review was performed on patients admitted to Dr. Cipto Mangunkusumo National General Hospital, Jakarta, with the diagnosis of SJS/TEN based on clinical features. The data were collected from paper-based and electronic health medical record database from January 2014 to December 2017. Diagnostic criteria were based on those proposed by Bastuji-Garin et al (Bastuji et al., 1993). Prognostic were assessed using the SCORTEN standard system. (Bastuji et al., 1993; Kim et al., 2012). The following datas were collected: demographic information, time from onset to admission, culprit drugs, underlying diseases, SCORTEN, extent of mucocutaneous involvement, laboratory data, treatments, complications, and mortality.

Institutional ethical committee clearance was obtained. All drugs that have been taken within six weeks before the onset of symptoms were considered as the culprit drugs (Yamane et al., 2007).

3 RESULTS

Of the total 34 medical records, 30 with complete data were selected and four with uncomplete data were excluded. The clinical characteristics of patients are available in table 1.

In our study, drug hypersensitivity was the causes in all SJS/TEN patients. The causative drugs are shown in figure 1. The most common culprit drug was anticonvulsants (carbamazepine, fenobarbital, haloperidol, gabapentin, pregabalin, lamotrigin, fenitoin, valproic acid), followed by antibiotics (cefixime, cotrimoksazole, ciprofloxacin, cefadroxil, meropenem levofloxacin, clindamicyn, amoxicillin), NSAIDs (paracetamole, mefenamic acid, ibuprofen, metamphyron), antituberculosis (rifampicin, isoniazide, pirazinamide, ethambutol), antiretroviral (tenofovir, nevirapine, stavudine, lamivudine), antiulcerative (ranitidin, omeprazole, lansoprazole), cough and flu medicines (ephedrine, phenylpropanolamine, phenylephrine, bromhexine, N-acetylcysteine), tramadol, antigout (allopurinol), antihistamine (cetirizine), anticancer (5-fu, cisplatin), antihypertension (captopril) , anticoagulant (transamin, aspilet), furosemide, antiparasites (pirimetamine, rescovulin), antiemetics (ondansetron, metoclopramide) and other drugs (activated attapulgite, loperamide, eperisone, fructus schizandrae extract).

Laboratory abnormalities showed increased amino transferase (AST, ALT), hiponatremia, anemia, leucocytosis, azotemia, hypoalbuminemia, thrombocytopenia, hyperglycemia, and increased procalcitonin. Patch test was performed in two patients, one patient had positive patch test for carbamazepine, and the other patient showed negative result.

All 30 cases (100%) were treated with intravenous methylprednisolone and fast tappering to oral methylprednisolone. Corticosteroids usage, length of stay, and mortality rate are shown in table 2.

Table 1. Clinical characteristics of SJS/TEN patients (n=30)

	n (%)
Age (years)	37.50 (15-70)
Gender	
Male	20 (66.7)
Female	10 (33.3)
Time from onset to admission (days)	3 (1-9)
Diagnosis	
SJS	11 (36.7)
SJS-TEN	12 (40.0)
TEN	7 (23.3)
Underlying diseases	
Epilepsi	9 (30.0)
Gastrointestinal problem	7 (23.3)
HIV infection	6 (20.0)
Chronic Kidney Disease	5 (16.7)
Hyperuricemia	5 (16.7)
Cardiovascular Disease	4 (13.3)
Respiratory Tract Infections	3 (10.0)
Stroke	3 (10.0)
Tuberculosis	3 (10.0)
Malignancy	2 (6.7)
Diabetes mellitus	2 (6.7)
Systemic Lupus Erythematosus	1 (3.3)
Hepatitis	
Mucosal involvement	
Oral	28 (93.3)
Ocular	21 (70.0)
Genitalia	11 (36.7)
SCORTEN	
≤1	3 (10.0)
2	8 (26.7)
3	11 (36.7)
4	5 (16.7)
≥5	1 (3.0)
Organ involvement and complications	9 (30)
Liver dysfunction	6 (20)
Renal dysfunction	3 (10)
Pulmonary infections	6 (20)
Sepsis	8 (26)
Electrolyte imbalance	

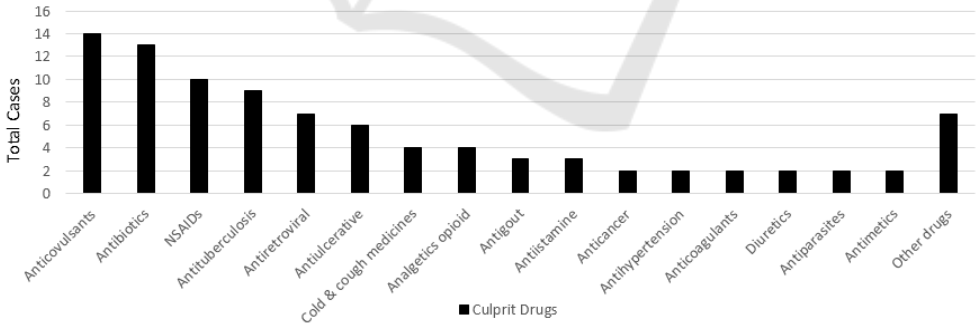

Figure 1. The causative drugs of SJS/TEN

Table. 2 Corticosteroids doses, length of stay and mortality in 30 patients

	SJS (n=11) n (%)	SJS-TEN *overlap* (n=12) n (%)	TEN (n=7) n (%)
Corticosteroids			
1 mg/kg/day	9 (81.8)	0 (0)	0 (0)
1.5 mg/kg/day	2 (18.2)	9 (75)	2 (28.6)
2 mg/kg/day	0 (0)	3 (25)	5 (71.4)
Length of stay (days)	6 (3-20)	8 (3-18)	11 (4-18)
Mortality rate	2 (18.2)	1 (8.3)	1 (14.3)

4 DISCUSSION

The median age was 37.5 years, which is lower than those reported from other countries in Asia such as Bangkok, Japan, Singapore, and Korea (Tan & Tay, 2012; Kim et al., 2012). Our study shows that females are affected with SJS/TEN more than males with a male-to-female ratio of 2:1, which was in agreement with earlier studies (Yamane et al., 2007; Kim et al., 2012). The causes of SJS/TEN were considered to be caused by an adverse reaction to drugs. The most common culprit drug was anticonvulsants, especially carbamazepine, followed by antibiotics, and NSAIDs, this is in agreement with study by Yamane et al[6]. The results may be because antibiotics and NSAIDs were available without prescription in Indonesia, and thus many patients with fever, headache, or other symptoms of infection purchased such drugs over the counter instead of consulting a doctor.

All 30 cases (100%) in our study were treated with intravenous corticosteroids, methylprednisolone. Methylprednisolone for SJS was 1-1.5 mg/kg/day prednisone equivalent dose. In SJS-TEN overlap and TEN group, the dose was increased to 1.5-2 mg/kg/day prednisone equivalent dose. These treatment is consistent with clinical guidelines for SJS/TEN treatment by Dr. Cipto Mangunkusumo National General Hospital and Indonesian Society of Dermatology And Venereology (ISDV) that recommends application of systemic corticosteroids 1-4 mg/kg/day. The differences between clinical guidelines from ISDV and our hospital is the preferences to use methylprednisolone rather than dexamethasone, because of the minimal adverse reactions. The corticosteroids doses were in agreement with guidelines by Gupta LK that recommends prompt withdrawal of the culprit drug, meticulous supportive care, and early (preferably within 72 hours) initiation of moderate to high dose of oral or parenteral corticosteroid (prednisolone 1-2 mg/kg/day or equivalent), tapered rapidly within 7-10 days (Gupta et al., 2016).

Additional therapies include supportive care with intravenous fluid drug, systemic antibiotics for prophylaxis, skin and wound care with 1% salicylic acid in cream or petrolatum and topical antibiotics for the secondary infections. No patient received other immunosuppressant or intravenous immunoglobulin. All patients were consulted to ophtamologist, dentist, otolaryngologist, and internist, consistent ith clinical pathway.

The length of stay in TEN group is higher than SJS and SJS-TEN overlap group. A total four cases died, two cases in SJS group, one case in SJS-TEN overlap, and one case in TEN group. Among SJS group, one patient both of patients who died had a severe underlying disease, one patient with end stage renal failure had complications such as septic shock and pneumonia, the other patient had a carcinoma sinonasal. The actual mortality rate in SJS group was higher (18.2%) compared to the predicted mortality rate (12.1%). The differences underlying diseases and infectious morbidity mainly influenced the mortality rate. In the SJS-TEN overlap group, one case with SCORTEN 4 died due to septic shock. The actual mortality rate in SJS-TEN overlap is lower (8.3%) than the predicted mortality rate (35.3%). One patient who died in TEN group was a 18 years old female with systemic lupus erythematosus, end stage renal failure, epilepsi, hypertension, ischemic heart disease and complications such us pneumonia and pleural efusion. The actual mortality rate in TEN group (14.3%) was lower than the predicted mortality score (35.3%).

5 CONCLUSIONS

Corticosteroids moderate or high doses and short period may contribute to reduced mortality rate in SJS/TEN without increasing secondary infection and serious sequele. The current treatments for SJS/TEN

in our hospital is consistent with the clinical pathway an clinical guidelines by Dr. Cipto Mangunkusumo National General Hospital and Indonesian Society of Dermatology and Venereology (ISDV). Further well-designed studies are required to compare the effect of corticosteroids treatment for SJS and/or TEN.

ACKNOWLEDGEMENTS

We express our gratitude to Dr. Cipto Mangunkusumo National General Hospital medical record staff for data collection.

REFERENCES

Bastuji-Garin, S., Rzany, B., Stern, R.S., Shear, N.H., Naldi, L. and Roujeau, J.C., 1993. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Archives of dermatology*, *129*(1), pp.92-96.

Fouchard, N., Bertocchi, M., Roujeau, J.C., Revuz, J., Wolkenstein, P. and Bastuji-Garin, S., 2000. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *Journal of Investigative Dermatology*, *115*(2), pp.149-153.

Gupta, L.K., Martin, A.M., Agarwal, N., D'Souza, P., Das, S., Kumar, R., Pande, S., Das, N.K., Kumaresan, M., Kumar, P. and Garg, A., 2016. Guidelines for the management of Stevens–Johnson syndrome/toxic epidermal necrolysis: An Indian perspective. *Indian Journal of Dermatology, Venereology, and Leprology*, *82*(6), p.603.

Kim, H.I., Kim, S.W., Park, G.Y., Kwon, E.G., Kim, H.H., Jeong, J.Y., Chang, H.H., Lee, J.M. and Kim, N.S., 2012. Causes and treatment outcomes of Stevens-Johnson syndrome and toxic epidermal necrolysis in 82 adult patients. *The Korean journal of internal medicine*, *27*(2), p.203.

Lee, H.Y., Tey, H.L., Pang, S.M. and Thirumoorthy, T., 2011. Systemic lupus erythematosus presenting as Stevens–Johnson syndrome and toxic epidermal necrolysis: a report of three cases. *Lupus*, *20*(6), pp.647-652.

Tan, S.K. and Tay, Y.K., 2012. Profile and pattern of Stevens-Johnson syndrome and toxic epidermal necrolysis in a general hospital in Singapore: treatment outcomes. *Acta dermato-venereologica*, *92*(1), pp.62-66.

Tripathi, A., Ditto, A.M., Grammer, L.C., Greenberger, P.A., McGrath, K.G., Zeiss, C.R. and Patterson, R., 2000, March. Corticosteroid therapy in an additional 13 cases of Stevens-Johnson syndrome: a total series of 67 cases. In *Allergy and asthma proceedings* (Vol. 21, No. 2, p. 101). OceanSide Publications.

Wang, L. and Mei, X.L., 2017. Retrospective analysis of stevens-johnson syndrome and toxic epidermal necrolysis in 88 Chinese patients. *Chinese medical journal*, *130*(9), p.1062.

Yamane, Y., Aihara, M. and Ikezawa, Z., 2007. Analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis in Japan from 2000 to 2006. *Allergology International*, *56*(4), pp.419-425.