MAGNITUDE, CAUSES & MORTALITY OF TEN, TEN-SJS & SJS IN ALERT HOSPITAL FROM MAY 2015 to MAY 2020G.C, ADDIS ABABA, ETHIOPIA

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ACRONYMS AND ABBREVIATIONS

- **A.A:** Addis Ababa
- **AAU:** Addis Ababa university
- **ALERT:** All African Leprosy Rehabilitation and Training center
- **E.C:** Ethiopian Calendar
- **FMOH**: Federal Ministry of Health
- **G.C**: Gregorian Calendar
- **HIV:** Human immune deficiency virus
- **HLA :** human leukocyte antigen
- **IRB:** Institutional review board
- **SJS :** Stevens-Johnson syndrome
- **TEN :**Toxic epidermal necrolysis
- **WHO:** World Health Organization

Abstract

Background: Epidermal necrolysis (EN) is rare with the overall incidence of 1 to 6 case per million person-years and 0.4 to 1.2 cases per million person-years, for SJS &TEN respectively. The mortality rate associated with EN varying from 10% for SJS to almost 50% for TEN. Increasing age, significant comorbidity, and greater extent of skin detachment correlate with poor prognosis.

Method: A retrospective study was conducted on EN patients visited ALERT hospital in the time frame mentioned above. The data was collected by reviewing the chart of patients with a clinical diagnosis of SJS, SJS-TEN&TEN between may2015-may2020. The collected data was analyzed.

RESULT: 50 patients with a diagnosis of SJS,SJS/TEN over lap & TEN were admitted during the study period.68% of the patients diagnosed with SJS, SJS-TEN & TEN are females. The most common affected age group is between 25-50 years of age. TEN, SJS/TEN & SJS was most frequently attributed to antibiotics .ciprofloxaciline being the leading causative agent. HIv infection is the most common comorbidity associated. Mortality rate of 14% for SJS/TEN & 2.5% for the TEN groups was found& Anemia was the most common complication seen.

Conclusion: Women and persons aged 25–50 years were the most affected groups within our study population, and drugs, especially ciprofloxaciline was the causative agent in 16% of the cases.

Keywords: SJS, TEN, SJS-TEN overlap,

1. INTRODUCTION

1.1. BACKGROUND

The skin represents the organ most commonly affected by adverse drug reactions. Some of these reactions are sever and may result in a significant mortality and morbidity. These include, in particular, Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) or Lyell's syndrome.

The estimated incidence of TEN and overlap of SJS/TEN (based on European epidemiology studies) range from an annual risk between 0.93 per million & 1.89 per million per year.

Based on a large European registry study, SJS is more common than TEN, and both SJS and TEN are more common in women than in men.
The incidence of SJS/TEN is also considerably higher in the HIV-positive population, and has been estimated at 1–2 per 1000 individuals in the population.
This could be due to the increased ingestion of drugs used in these patients, the immunodeficiency itself, and/or the associated infections experienced in these patients.

Drugs are the leading reported cause of TEN, with the risk of a hypersensitivity reaction mainly in the first few weeks of the drug ingestion.
A large multi-national case-control study conducted in Europe identified strong associations between SJS/TEN and several drugs, including anti-infective sulphonamides, allopurinol, carbamazepine, phenobarbital, nevirapine, lamotrigine, phenytoin, and oxicam-non steroidal anti-inflammatory drugs (NSAIDs) .
TEN has also been reported to occur following measles-mumps rubella vaccination and mycoplasma pneumonia infection—particularly in children.

Such reactions are characterized by confluent erythema and areas of skin detachment reflecting epidermal necrosis because of keratinocyte apoptosis.
There is usually erosive mucosal involvement of the oral, nasal, ocular, genital or anal area.

A few days before the skin manifestations appear, there might be flu-like symptoms with fever, sore throat and ocular pain.
Visceral involvement is also possible, particularly with pulmonary and digestive complications.

The main difference between SJS and TEN is represented by the extent of dermo-epidermal detachment.
When the detachment is less than 10%, the reaction is classified as SJS; if the detachment is equal to or greater than 30%, it is classified as TEN. The intermediate stages are classified as SJS-TEN overlap. The reaction usually appears within 4–28 days after starting a new drug.
The mortality rate associated with EN varying from approximately 10% for SJS to almost 50% for TEN. The disease runs an unpredictable course.
Mortality risk can be calculated by applying a severity-of-illness score specifically developed for predicting the clinical outcome of TEN (SCORTEN).

During the acute phase, the most common complication of EN is sepsis. The epithelial loss predisposes these patients to infections, which are the main causes of mortality. Multisystem organ failure and pulmonary complications are observed in more than 30% and 15% of cases, respectively.
The chronic sequelae of SJS have been discussed in a number of studies published over the past decade. Mucosal involvement consisting of oral

frenulum –like fibrotic bands or vulvovaginal synechiae has also been noted.
Although rare, chronic pulmonary complications, including bronchiolitis obliterance, chronic bronchitis& interstitial lung disease have been reported.

Prompt withdrawal of offending agent(s) is associated with an increased rate of survival in patients with EN.

Primary prevention is only feasible in populations where a strong association has been established between a simple genetic maker and the risk of EN.
That is the case for HLA-B□1502 and EN induced by carbamazepine in persons of Southeast Asian ancestry. Secondary prevention is important for patients who experienced EN and are reluctant to take any medication

2. OBJECTIVES

2.1. General Objectives

To determine the magnitude, causes and mortality due to epidermal necrolysis in alert hospital over a five year period.

2.2.Specific Objectives

1, to determine socio demographic characteristics of patients with EN
2, to determine the outcomes of patients diagnosed with EN

3. METHODOLOGY

After obtaining letter of approval for research proposal from AAU, College of Health Sciences, and department of Dermatovenereology ethical review committee, data collection was started.

3.1. Study Design

Hospital based, retrospective study design was used

3.2. Eligibility

3.2.1. Inclusion criteria

All patients of either gender with clinical diagnosed of SJS, SJS-TEN & TEN

3.2.2. Exclusion criteria

Those patients with a diagnosis of autoimmune blistering disease, staphylococcal scaled skin Syndrome (SSSS) or other types of sever drug eruption was excluded from the study

3.3. Sample size determination & Sampling procedure

3.3.1. Sample size determination

All patients with the diagnosis SJS, SJS-TEN OVERLAP & TEN who were admitted during the study period were included.

3.3.2. Sampling technique

Charts of all patients with a diagnosis of SJS, SJS-TEN OVERLAP & TEN who were admitted during the study period were reviewed & included in the study. The charts were accessed by using card number & name from wards (3 & 4) registration book.

3.4. Data collection procedures (instruments, personnel, data quality control)

The data were collected from dermatology ward registration book & Patient charts by using a structured data capture sheets or check lists. Two selected data collectors were assigned for data collection. The data collectors were given 2 days training on the check list

For record review to equip them with the necessary skill .They were continuously supervised by the principal investigator during data collection process. Check lists were prepared in English language, pretested & necessary modifications were made. The capture sheet used for data collection is found in annex. Data collected were doubly entered the some day as collected. This helped to address any inconsistencies regarding wrong entries.

3.5.Study variables

Dependent: Mortality

Independent: Sex, age, PR co-morbidities, HIV-status ,medication used in the preceding 8 weeks; classification as SJS, SJS/TEN overlap and TEN,BSA,Urea

3.6. Operational definition:

1, SJS: epidermal detachment of <10% of the body surface in association with widespread erythema and/or dusky red macules.

2, SJS/TEN overlap: epidermal detachment of 10–30% of the body surface plus widespread dusky red macules.

3, TEN: epidermal detachment of >30% of the body surface coupled with widespread dusky red macules.

4, Causative agent, is defined as a drug that is taken up to 3 months earlier before development of symptoms. In case of drug causality Alden score will be used to identify the probable & very probable causality.

3.7. Data processing and analysis

3.7.1. Data processing

Each completed check list was checked for completeness before data entry manually. Then the data was coded & entered into a computer by using EPI info version 7 & further clean-up was made to check accuracy & consistency. Data cleaning was done by removing duplicated data invalid data & any error identified was corrected. Finally data was exported to SPSS VERSION 20 for further cleanup & recording was done.

3.7.2. Data analysis procedure

Data was coded & entered by EPI data &transferred to SPSS version 20 computer programs for analysis. socio-demographic Data, medical information ,timing from disease onset to admission, suspected drug allergy history, TBSA, medical comorbidities, physical examination, laboratory data, associated complications, duration of hospital stay, and observed mortality of patients with a diagnosis of SJS,SJS-TEN & TEN patients was summarized & presented by descriptive analysis. Multi-variant analysis was done to see the relationship between complications & associated factors.

4. RESULT

4.1. Socio-Demographic Characteristics

A total of 59 patients were included in the study, 9 patients were excluded from the study because of misdiagnosed(three patients with SLE, two patients with Para neoplastic pemphigus ,two patient with erythema multiforma major, one patient with pemphigus fallacious &one patient with pemphigus vulgaris). From the 50 Patients diagnosed with SJS,SJS/TEN & TEN,34 where females(68%) &16 where males(32%).aged between 15 & 62years. The largest number of patients was those aged between 25 and 50 years (36,72%), compared with <25years (6,12%), 50-75years (8,16%). 31 patients(62%) had mucous involvement, involvement of the oral and lip mucosa (25, 50%), oral &ocular mucosa (4, 8%), and oral & genital mucosa (2, 4%). The time from the beginning of the illness to admission was between two and 30 days . A total of 40 of 50 patients (80%) where admitted with TEN, 7(14%) patients with SJS/TEN overlap and 3(6%) patients with SJS.

The average lengths of hospital stay of patients were 8.5 days.

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Table 1: frequency of mucosal involvement

Site of involvement	Frequency & percent of patients
Oral mucosa	25(50%)
Oral & genital mucosa	2(4%)
Oral & ocular mucosa	4(8%)

Table 2: Disease characteristics of the study population

Sub class	Frequency	Valid percent
TEN	40	80%
TEN/SJS	7	14%
SJS	3	6%

4.2.The causative drugs

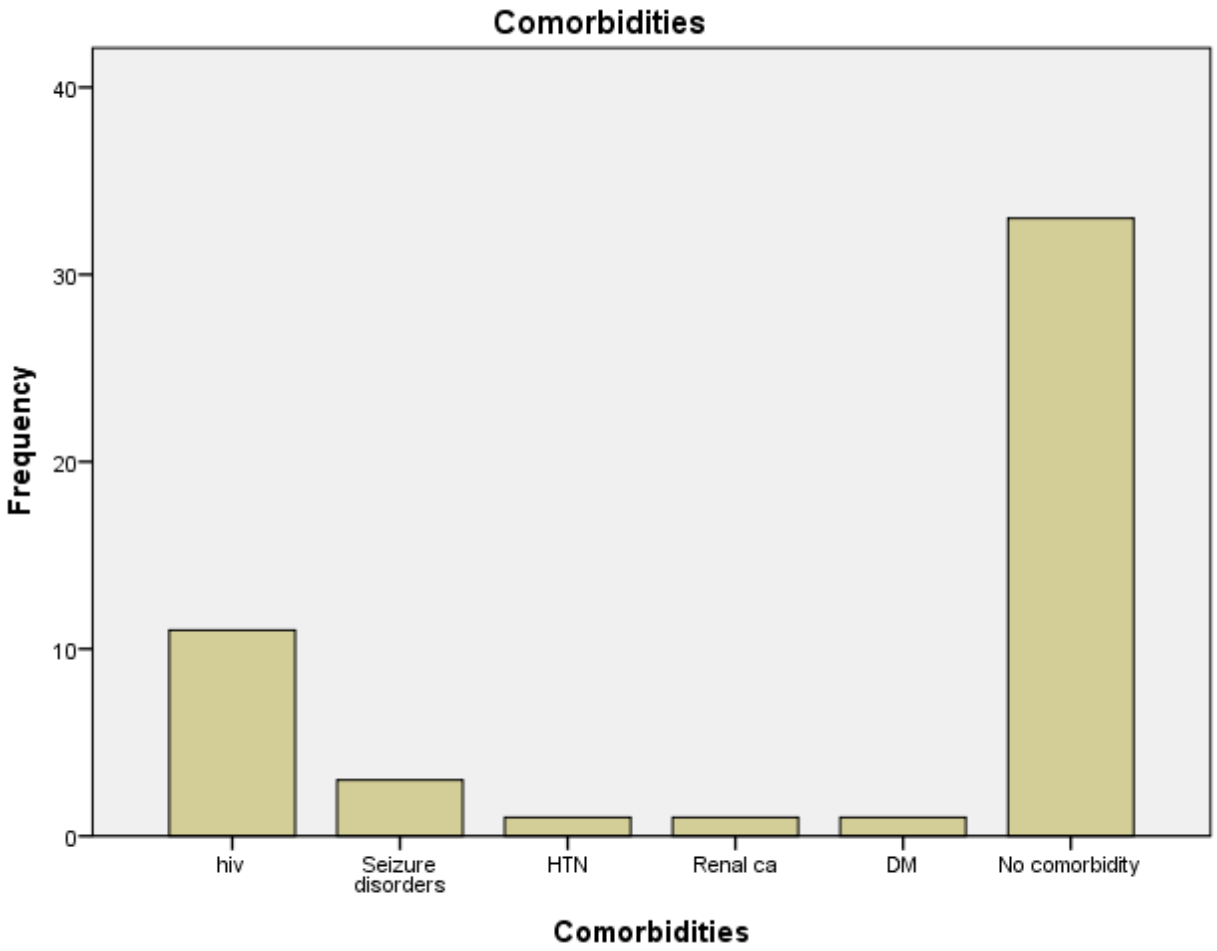
For this group, TEN,SJS/TEN & SJS was most frequently attributed to antibiotics (24, 46%), unspecified drugs (13,26%) , anticonvulsants (5, 10%), nonsteroidal anti-inflammation drugs (3, 6%), allopurinol (1, 2%), ART (1, 2%) &Tramadol(1,2%; moreover, 9 patients (18%) developed SJS/TEN after taking mixed drugs.

Table 3:List of causative drugs

Type of drug	frequency	percent
Ciprofloxaciline	8	16.0%
Unknown	13	26%
Carbamazepine	3	6%
Phenobarbitone	1	2%
Iboprophen	1	2%
Ceftriaxone	1	2%
Amoxaciline	3	6%
Allopurinol	1	2%
Sorafenib	1	2%
Doxycycline	2	4%
Phenytoin	1	2%
Diclopenac	2	4%
Tramadol	1	2%
ART	1	2%
Mixed antibiotics	9	18%

4.3. Comorbid medical conditions

Comorbidities at the time of hospital admission included HIV infection (11, 22%), epilepsy (3, 6%), diabetes mellitus (1, 2%), active malignancy (1, 2%), chronic kidney disease (1, 2%), hypertension (1,2%).



4.4. Analysis of mortality

Mortality rate of 14% for SJS/TEN & 2.5% for the TEN groups was found.

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. Table 4 – Analysis of the two Deceased cases of SJS/TEN

Case no	Age & sex	Length of hospital stay	Causative drugs	Disease severity	comorbidities	Cause of death
1	25,F	10 days	phenobarbitone	TEN	epileptic	SEPSIS
2	22,F	03 days	ART	SJS/TEN	RVI	SEPTIC SHOCK

4.5. Complications

Anemia was the most common complication seen in12 (24%), electrolyte disturbance was seen in 4(8%) cases of hyponatrima ,hypokalemia 1(2%) . Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increases were found in 5 (10%). Hyperglycemia was observed in 7 cases (14%) . Acute kidney injury was observed in 3(6%) cases with raised creatinine & BUN. 3(6%) patients had developed sepsis. 4 patients (8%) had pneumonia. 2(4%) patients had hypovolemia

5. Discussion

There were a total of 50 patients admitted for SJS,SJS/TEN & TEN out of 1930 ward admitted patients over a period of 5 years. Making the magnitude of this disease 0.026 from the totally admitted patients. This result mirrors the scarcity of this disease observed in other studies [1, 2, 4]. 68% of cases were in women, while 32% were in men. This female predominance is similar to findings from other studies done [1,2,4] . Numerically, there were more females than males with SJS , TEN/SJS & TEN disease subtypes at 100% versus0%,57% versus43% and 64% versus 32%, respectively.

This trend has been seen in another study's, where more females had SJS and TEN disease subtypes at 30.4 versus 16.5% and 20.0 versus 13.9%, respectively [1]. There were, however, no statistically significant associations between patients' sex on the development of various disease subclasses.

The largest number of patients was those aged between 25 and 50 years (36,72%), compared with <25years (6,12%), 50-75years (8,16%). There were also more patients in this age category across the various disease subtypes, a finding that was replicated in the study by Kenneth Irungu et al. [1] & Saka et al. [4] .Our results on the most prevalent age group conflict with other studies that show most patients being elderly and attributing this to reduced drug clearance [2]. The largest affected age group being between 25 & 50 in our study could possibly be attributed to epidemiology of HIV infection& frequent self-prescribing of medicine in this age GROUP.

The causative agents of SJS/TEN were determined by checking the original patient medical files since it was a retrospective study. These were considered accurate due to the following reasons: the drugs implicated in our study were consistent with those in other studies. For other drugs like anti-cancer drugs, there is literature implicating them
to cause SJS/TEN . There was a reasonable time lapse between exposure to the drugs and development of symptoms.

The most frequent causative agents in our study were antibiotics, unspecified drugs & antiepileptic drugs. Antibiotics &antiepileptic being the commonest causative agents, this is similar to those previously reported in the literature [2,3,7]. There was a high number of SJS/TEN cases (n = 11) caused by unidentified drugs, no records were available to identify them. Higher number of unknown drugs is also seen in previous studies [1,8] . Among all the causative antibiotics, fiuoroquinolone ranked first (8, 16%) and B-lactam antibiotics followed (3, 6%). At least 3(6%) cases were sensitized by carbamazepine; it was the most common antiepileptic drugs. . Among nonsteroidal anti-inflammatory drugs, diclopenac was the most common causative drug, with a total of 2(4%) cases. There was a single case of sorafenib(anticancer drug) as a causative agent. There are few case reports of sorafenib caused TEN prior to ours. In addition, some patients took mixed medications before the onset of SJS/ TEN, which interfered with the assessment of specific allergenic drugs. Herbal medications sought from traditional healers may have unknown ingredients and undocumented phytochemical extracts. These herbal medications have been shown to cause SJS/TEN in other studies [1,7] and in our study this was not seen in any of the cases. Considering the rampant use of herbal medicines locally. We attributed this to under-reporting of their use by patients to clinicians.

Mortality rate of 14% for SJS/TEN group & 2.s% for the TEN groups was found. The overall mortality rate in this study was lower than reported in the literature [2, 5]. The lower mortality may be associated with a combination of factors, like the patients admitted to our department in less-severe condition.

SJS/TEN extensively involves the skin and mucosa, causing blistering, erosions, and exfoliations of skin and mucous membranes so that excellent skin care and other supportive care are pressingly needed. In addition to skin conditions, the emergence of various complications poses a greater challenge to clinical practice and directly affects the outcome of the disease

Infection: This is the life-threatening problem in the treatment of SJS/TEN, increasing organ injuries and the cost of treatment (expensive antibiotics, prolonged hospitalization). Both deaths in this study were attributed to sepsis. Controlling infection presents a great challenge to dermatologists.

Hyperglycemia: In the course of the disease, 7cases (14%) had elevated blood sugar (_7.0 mmol/L) . excessive hyperglycemia can increase the risk of infection and lead to ketosis, hypernatremia, and other complications.

6. Limitations

The study was limited in scope in that it was conducted at only one tertiary care hospital. A multi-center approach involving a large sample size would go a long way in educating us about the causal associations, the morbidity patterns, and the associated mortality rates.

Information bias arose since the cases were already classified as SJS, SJS/TEN or TEN according to the medical records. It was relied on reported data and the verification was difficult because for all of these patients BSA involved was not recorded.
It was difficult to compare the mortality reported with the SCORTEN of the patients, because SCORTEN was not recorded for all of the patients.
ALDEN score was not used for mixed drugs because of lack of detailed drug history recorded on the medical records.
For those patients with unspecified drug history, it was not possible to trace the responsible drug .

7. Conclusion

Epidermal necrolysis are rare severe cutaneous reactions and the most frequently observed disease subtype in our study was TEN. Women and persons aged 25–50 years were the most affected groups within our study population, and drugs, especially ciprofloxaciline, was the causative agent in 16% of the cases. Further studies are warranted in greater sample sizes across Ethiopia, comparing patient characteristics with the general population, in order to reach statistical significance and to determine any other predisposing factors to SJS/TEN.

8. Recommendation

A multi-center prospective study involving a large sample size is recommended.
Also for SJS, SJS/TEN & TEN patients BSA involved should be recorded in order to avoid information bias. SCORTEN should be recorded for all of the patients with epidermal necrolysis .lastly detailed drug history should be recorded in order to identify the causative agent.

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11. Annex

Annex one: questionnaire/data capture sheet

Part I. socio-demographic character

No	Question	response	code
1	Age of the patient		A1
2	sex		A2

Part 2. Disease characteristics of the study population

NO	Question	response	code
	Duration of illness		B1
	Drug intake within the last 3 months If yes,how many drugs,time gap between each drug &onset of symptome		B2
	Sub class of the disease(SJS,TEN or SJS-TEN overlap		B3
	Involvement of mucosal membrane If yes ,how many		B4
	Was there any complication e.g sepsis,pneumonia,scaring		

Part 3. Table – Deceased cases of SJS/TEN

NO	Question	response	code
	age		C1
	sex		C2
	Hospital stay(days)		C3
	Causative drug		C4
	Comorbidity		C5
	SJS,TEN,SJS-TEN overlap		C6
	Cause of death		C7

Part 4. Probable causative agents

No	Question	Response(if the answer is yes, specify the drug)	code

	Is there probable causative agent		D1

Part 5. Investigations

No	question	response	*code*
	WBC N% Hg Hct		E1 E2 E3 E4
	BUN Creatinine Na+ K+ Ca+		E5 E6 E7 E8 E9
	SGOT SGPT		E10 E11