Incidence, causative drugs, and economic consequences of drug-induced SJS, TEN, and SJS–TEN overlap and potential drug–drug interactions during treatment: a retrospective analysis at an Indonesian referral hospital

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Background: Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute life-threatening adverse drug reactions (ADRs) that are commonly caused by medications. Apart from their contribution to morbidity and mortality, these diseases may also present substantial consequences on health care resources. In this study, we aimed to identify the incidence, causative drugs, and economic consequences of these serious ADRs and potential drug–drug interactions (DDIs) during treatment.

Methods: A retrospective study that included 150 patients diagnosed with drug-induced SJS, SJS–TEN overlap, and TEN, from 2009 to 2013 in a referral hospital in West Java Province, Indonesia, was conducted to analyze the causative drugs, cost of illness (COI) as a representation of economic consequences, and potential DDIs during treatment.

Results: The results showed that analgesic–antipyretic drugs were the most frequently implicated drugs. The COIs for SJS, SJS–TEN overlap, and TEN patients were 119.49, 139.21, and 162.08 US dollars per day, respectively. Furthermore, potential DDIs with several therapeutic medications and corticosteroids used to treat SJS, SJS–TEN overlap, and TEN were also identified.

Conclusion: This study showed that analgesic–antipyretic was the major causative drug which contributed to SJS, SJS–TEN overlap, and TEN. Furthermore, our results also showed that SJS, SJS–TEN overlap, and TEN may cause considerable financial consequences to patients.

Keywords: Stevens–Johnson syndrome, toxic epidermal necrolysis, adverse drug reactions, cost of illness

Introduction
Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute life-threatening adverse drug reactions (ADRs) characterized by epidermal detachment and mucositis.¹ The basic difference between SJS and TEN is the percentage of body surface affected, and SJS affects <10% of the body surface, SJS–TEN overlap involves 10%–30% of the body surface, and TEN affects >30% of the body surface area.²,³ The incidence varies from 1 to 6 cases and 0.4 to 1.2 cases per million annually for SJS and TEN, respectively.⁴,⁶ However, the incidence is higher among people living with HIV/AIDS.⁷
Drugs are identified as the main etiologic agents of SJS, TEN, and SJS–TEN overlap syndrome. Based on RegisSCAR/EuroSCAR registries, the highest risk drugs include allopurinol, carbamazepine, cotrimoxazole, and other anti-inflammatory drugs (NSAIDs), phenobarbital, and phenytoin. Moderate-risk drugs include cephalosporins, macrolides, quinolones, tetracyclines, and acetic acid-type NSAIDs. Low-risk drugs, that in previous studies, were not associated with a measurable risk, including beta-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, sulfonamide-based thiazide diuretics, sulfonylurea anti-diabetics, insulin, and propionic acid–type NSAIDs.8,9

Despite the fact that the incidence of SJS or TEN is acute life-threatening, the condition may also lead to significant financial consequences for the patients.10 Therefore, identification and withdrawal of drugs suspected to cause SJS or TEN are important.11 In Indonesia, however, little work has been conducted to identify the prevalence, causative drugs, and economic consequences caused. Accordingly, it is important to explore the best strategy to find as many relevant studies as possible. Thus, this study was aimed to identify the number of incidence, causative drugs, economic consequences, and potential drug–drug interaction (DDI) during treatment of these serious ADRs.

Methods
Data collection and study populations
We conducted a retrospective study in a referral hospital in West Java Province, the most populous Indonesian province, that is covered with 46.7 million population.12 Medical records from patients diagnosed with drug-induced SJS (ICD10 code L50.1), TEN (L50.2), or SJS–TEN overlap (L50.3) syndrome from January 1, 2009, to December 31, 2013, were recalled and included in the study. A data collection sheet was designed for the purpose of organizing collected data from patient records. Data included patient demographics, disease progression, duration of hospital stay, detailed treatment regimen, and suspected causative drugs as specifically mentioned in medical records by treating physicians. Incomplete patient records and records of patients referred with SJS, TEN, or SJS–TEN overlap syndrome from other hospitals were excluded from the study. Incomplete patient records that excluded were due to insufficient data and improper record, that is missing of suspected causative drug from the treating physicians, and incomplete medical treatment records. Two authors (RA and DPD) independently assessed the medical record for inclusion to the study. Differences were discussed and consensus reached.

Ethical approval for the study was obtained from the Ethical Committee for Health Research of Hasan Sadikin Hospital, Bandung, Indonesia No: LB.04.01/A05/EC/536/XII/2014. The study was conducted according to the guidelines of the Declaration of Helsinki. Written informed consent was not required because this was a retrospective observational study. No medical interventions were performed during the study. All ethical considerations were followed. Patient files were processed anonymously. No personal data were collected.

Analysis of economic consequences
The economic consequences of SJS, TEN, and SJS–TEN overlap were calculated using cost of illness (COI) for each patient. A societal perspective was applied in this study by considering the total direct medical cost and indirect cost of lost productivity. The direct medical cost was calculated by considering the price of all medications received, expenses (preparation and administrative costs, monitoring costs, and the costs of treatment for adverse events and treatment failures), the cost of action, and the hospital room rate (including fees for doctors, nurses, pharmacies, and nutritionists that differ depending on the severity and treatment received by each patient). The potential loss of productivity was calculated using a report from the Indonesian Statistical Agency for average monthly income of people living in Bandung City, Indonesia,13 that adjusted to the total length of hospital stay of each patient.

Currency was converted from the Indonesian rupiah (IDR) to the US dollar (USD) using the World Bank’s purchasing power parity (PPP) conversion factor, which is the number of units of a country’s currency required to buy the same amount of goods and services in the domestic market as the USD would buy in the USA.14

Analysis of drug interaction
The analysis of potential DDIs was performed to analyze the interactions of SJS/TEN treatment with the drugs suspected of being the cause of SJS/TEN and interactions of concomitant therapy between SJS/TEN treatment with drugs used to treat the original disease not related to SJS/TEN. Identification of DDIs was performed with Truven Health Analytics Micromedex®, a registered subscription database, and Drugs.com™ and Medscape.com™, 2 free databases. Micromedex provides reference information for drug management for diseases and conditions, as well as toxicology and patient education.
identifies potential DDIs, including the mechanism of DDIs, potential adverse reactions, their clinical consequences, and level of documentation available for the interaction (excellent: controlled study have clearly established; good: documentation strongly suggests the interactions; fair: available documentation were poor). Drugs.com is a free database powered by Wolters Kluwer Health, the American Society of Health-System Pharmacists, Cerner Multum, and Micromedex, which are leading medical information databases. Medscape.com provides online medical information and educational tools, including a drug interaction checker.

Results
Number of incidence
From the records of 150 patients diagnosed with SJS, SJS–TEN overlap, and TEN during 2009–2013, a total of 101 medical records were included in this study. The details of the selection process are shown in Figure 1. The demographics of the patients included in this study are shown in Table 1.

Economic consequences
The total economic loss from the 101 cases of SJS, SJS–TEN overlap, and TEN during the study period was estimated at 131,763.82 USD, including 77,786.64, 29,179.29, and 24,797.89 USD from SJS, SJS–TEN overlap, and TEN, respectively. For SJS, SJS–TEN overlap, and TEN, the average cost per patient was 1,111.24, 1,823.71, and 1,653.12 USD, respectively, and the average direct cost per patient was 974.86, 1,630.91, and 1,504.07 USD, respectively. A detailed breakdown of the cost calculation and average spending per patient per day for SJS, SJS–TEN overlap, and TEN can be seen in Table 2.

Causative drugs
Each drug implicated in SJS, SJS–TEN overlap, and TEN in the study can be seen in Table 3. As shown, analgesic–antipyretic drugs (acetaminophen) were reported most frequently, followed by antibiotics (amoxicillin, cotrimoxazol, and ciprofloxacin), tuberculosis drugs (rifampicin, ethambutol, isoniazid, and pyrazinamide), anti-HIV medications (nevirapine, lamivudine, and zidovudine), and NSAIDs (mefenamic acid, ibuprofen, and aspirin). In Table 3, the implicated drugs were compared to other reports from Japan, Europe and Israel, France, sub-Saharan Africa, and Senegal.

Potential DDIs
The results of DDI analysis from 3 of the databases showed discrepancies in the classification of severity and mechanism of interaction (Table 4A and B). However, we found 29 cases identified by all 3 databases for potential interactions of SJS/TEN treatment with the drugs suspected of being the cause of SJS/TEN and 87 cases identified by all 3 databases for potential interaction of concomitant therapy between SJS/TEN treatment with drugs used to treat the original disease not related to SJS/TEN. The most common potential DDIs of corticosteroids with the drugs suspected of being the cause of SJS/TEN identified by the 3 databases were dexamethasone–rifampicin (24.14%), dexamethasone–ciprofloxacin (20.69%), dexamethasone–ibuprofen (20.69%), dexamethasone–mefenamic acid (17.24%), and dexamethasone–aspirin (10.34%). Meanwhile, the most common potential DDIs of concomitant treatment of corticosteroids with drugs used to treat the original disease not related to SJS/TEN were dexamethasone–ofloxacin (12.64%), dexamethasone–levofloxacin (10.34%), dexamethasone–ciprofloxacin (8.05%), dexamethasone–efavirenz (6.90%), and dexamethasone–phenobarbital (6.90%).

Discussion
The drugs most frequently implicated in cases of SJS, SJS–TEN overlap, and TEN in our study were analgesic–antipyretic...
the COI of SJS patients in our study was 119.49 USD per
day for only SJS-related medication, not the cost of treatment
of their primary diagnosis before SJS diagnosis. Meanwhile,
with the involvement of more body surface area, the daily
COI for SJS–TEN overlap and TEN patients increases to
139.21 and 162.08 USD, respectively. These are higher than a
previous report from Gujarat, India, that reported 15.16,
18.04, and 22.96 USD per day for SJS, SJS–TEN overlap,
and TEN, respectively, after converted to USD using the
World Bank’s PPP conversion factor.10,14 The Gujarat study,
however, only calculated the cost of medications, diagnosis,
and consumables used during the hospital stay.

The average hospital stay in this study was ~9.3, 13.1, and
10.2 days for SJS, SJS–TEN overlap, and TEN, respectively.
The number of hospital stays may associate to the different
levels of severity and complexity of SJS, SJS–TEN overlap,
and TEN patients. Patients with TEN have a more severe dis-
ease and are likely to have longer hospital stay than patients
with SJS. However, these findings were less significant than
those reported in a previous study in Thailand.29 In particular,
a longer hospital stay was observed among SJS–TEN patients
than among TEN patients in our study. This finding could
be explained by the fact that 8 of 15 TEN patients were died
within a short period of time, thus resulting in a shorter
average hospital stay than SJS–TEN patients. This result is
in line with the latest study from Thailand.29 In contrast to
the average hospital stay in this study, TEN patients had the
highest COI of the patients studied. This result is probably
because TEN patients were likely to be more complicated
recoveries than SJS and SJS–TEN patients.

There is currently no specific treatment for TEN or SJS
because of their complex pathogenesis. Although systemic
corticosteroids and intravenous immunoglobulin are contro-
versial, they are still the main treatment methods in many
countries,30 including Indonesia. In our study, most cases
were treated with corticosteroids. Although corticosteroids
are controversial for the treatment of SJS and TEN due to
the reports on the increased risk of secondary infection and
delay in epithelialization,31–33 they are still beneficial when
started early and in an appropriate dose range.34 The use
of corticosteroids may be based on the idea that they may
inhibit immunological responses by suppressing interferon
gamma-mediated apoptosis and the functions of cytotoxic
T lymphocytes.35 The corticosteroids, however, have to be
used cautiously for the treatment of SJS, SJS–TEN overlap,
and TEN, as in our study, they have the potential for DDIs
with medicines used to treat the primary disease. The most
common potential DDIs of corticosteroids found in this

### Table 1 Demographic characteristics of patients included in this study

<table>
<thead>
<tr>
<th>Demographic parameters</th>
<th>SJS (n=70)</th>
<th>SJS–TEN overlap (n=16)</th>
<th>TEN (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Female</td>
<td>37</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>30.15±16.45</td>
<td>26.75±18.65</td>
<td>25.45±15.82</td>
</tr>
<tr>
<td>LOS (days)</td>
<td>9.33±6.68</td>
<td>13.19±6.91</td>
<td>10.20±7.66</td>
</tr>
</tbody>
</table>

Note: Data presented as number or mean ± SD.

Abbreviations: SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; LOS, length of hospital stay.

(Table 3). Although not in the top 5 of drugs most implicated
in this study, antiepileptic carbamazepine counted for up to
3.92% of all the drugs implicated. Carbamazepine-induced
SJS/TEN is reported to be associated with HLA allele
B*1502,22 whose frequency has been reported to be as high
as 11.6% in Western Javanese population.21 Therefore, this
should also be seriously considered, especially as carbama-
izepine also used in off-label prescription.24

It has been reported that the treatment of ADR-related
diseases requires substantial financial resources, as many
countries may spend 15%–20% of hospital budgets for this
purpose.25,26 Considering the potentially serious consequences,
SJS, SJS–TEN overlap, and TEN may have a significant clinical
and economic impact on patients. A previous study reported
that patients with ADRs may stay in the hospital 12 days lon-
ger than those without ADRs.27 This can significantly affect
those in developing countries due to the damaging effects of
ADR-related diseases on the socioeconomic progress of those
countries. SJS, SJS–TEN overlap, and TEN will increase
treatment costs due to prolonged hospital stays, additional
clinical investigations, and treatments. As seen in Table 2,

### Table 2 Economic cost calculation and average spending per patient per day for each case of SJS, SJS–TEN overlap, and TEN in this study

<table>
<thead>
<tr>
<th></th>
<th>SJS</th>
<th>SJS–TEN overlap</th>
<th>TEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of hospital stay (days)</td>
<td>9.3</td>
<td>13.1</td>
<td>10.2</td>
</tr>
<tr>
<td>Direct medical cost</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescribed medicine related to SJS, SJS–TEN overlap, and TEN treatment (USD)</td>
<td>163.04</td>
<td>280.49</td>
<td>279.39</td>
</tr>
<tr>
<td>Medical treatment cost (USD)</td>
<td>117.32</td>
<td>249.17</td>
<td>284.07</td>
</tr>
<tr>
<td>Other medical supporting cost (USD)</td>
<td>216.39</td>
<td>426.85</td>
<td>418.25</td>
</tr>
<tr>
<td>Hospital stay and administraition (USD)</td>
<td>478.11</td>
<td>674.40</td>
<td>522.37</td>
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<tr>
<td>Indirect medical cost</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potential productivity lost (USD)</td>
<td>136.38</td>
<td>192.80</td>
<td>149.12</td>
</tr>
<tr>
<td>Total COI (USD)</td>
<td>1,111.24</td>
<td>1,823.71</td>
<td>1,653.20</td>
</tr>
<tr>
<td>COI per day of hospital stay (USD)</td>
<td>119.49</td>
<td>139.21</td>
<td>162.08</td>
</tr>
</tbody>
</table>

Abbreviations: SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; USD, US dollar; COI, cost of illness.
### Table 3 Drugs implicated in SJS, SJS–TEN overlap, and TEN, their incidence in this study, and comparison with other reports

<table>
<thead>
<tr>
<th>Our study</th>
<th>Other reports</th>
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<tr>
<td>Total no of cases</td>
<td>101</td>
</tr>
<tr>
<td>SJS</td>
<td>70</td>
</tr>
<tr>
<td>SJS–TEN overlap</td>
<td>16</td>
</tr>
<tr>
<td>TEN</td>
<td>15</td>
</tr>
<tr>
<td>Death rate (%)</td>
<td>10.9</td>
</tr>
</tbody>
</table>

**Drugs implicated**

1. Analgesic–antipyretic (13.40%)
   - Anticonvulsants
   - Allopurinol
   - Antibiotics
   - Sulfonamides
2. Antibiotics (11.76%)
   - Carbazepine
   - Nevirapine
   - Sulfonamides
3. Tuberculosis drugs (9.80%)
   - NSAIDs
   - Cotrimoxazole
   - NSAIDs
   - Tuberculosis drugs
4. Anti-HIV (6.54%)
   - Allopurinol
   - Nevirapine
5. NSAIDs (5.23%)
   - Antitussive
   - Phenobarbital
   - Anticonvulsants
   - Aminopenicillins

**Note:** The “–” indicates that this reference only provided 4 types of drugs.

**Abbreviations:** SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; NSAIDs, non-steroidal anti-inflammatory drugs.

### Table 4 Results of DDI analysis of (A) corticosteroids with the drugs suspected of being the cause of SJS/TEN and (B) concomitant treatment of corticosteroids with drugs used to treat the original disease not related to SJS/TEN, identified using the Micromedex, Drugs.com, and Medscape.com websites

<table>
<thead>
<tr>
<th>DDI databases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micromedex</td>
</tr>
</tbody>
</table>

(A)

| Number of patients with potential DDIs | 32 (31.68%) | 42 (41.58%) | 46 (45.54%) |
| Number of patients without potential DDIs | 69 (68.32%) | 59 (58.42%) | 55 (54.46%) |
| Number of interactions | 35 | 46 | 54 |

<table>
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<th>Severity</th>
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<tbody>
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<td>Contraindicated</td>
</tr>
<tr>
<td>Major/serious</td>
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<tr>
<td>Moderate/significant</td>
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<tr>
<td>Minor</td>
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<table>
<thead>
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<th>Mechanism</th>
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</thead>
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<td>Pharmacokinetic</td>
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<tr>
<td>Pharmacodynamic</td>
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<tr>
<td>Pharmacokinetiic/pharmacodynamic</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Onset</th>
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<tbody>
<tr>
<td>Delay (after 24 hours)</td>
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<tr>
<td>Rapid (until 24 hours)</td>
</tr>
<tr>
<td>Not specified</td>
</tr>
</tbody>
</table>

(B)

| Number of patients with potential DDIs | 49 (48.51%) | 34 (33.66%) | 27 (26.73%) |
| Number of patients without potential DDIs | 52 (51.49%) | 67 (66.34%) | 74 (73.27%) |
| Number of interactions | 113 | 250 | 268 |

<table>
<thead>
<tr>
<th>Severity</th>
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(Continued)
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Disclosure
The authors report no conflicts of interest in this work.

References


