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# Clinicoepidemiological Profile of Severe Cutaneous Adverse Drug Reaction: A Retrospective Study

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**ABSTRACT**

**Background:** Drug eruption were varied from mild to severe reaction. Few studies have assessed the severe cutaneous adverse drug reaction (SCADR), especially in the setting of general hospital. **Purpose:** To evaluate clinicoepidemiological profile of SCADR at Dermatology and Venereology Ward Dr. Soetomo Hospital, Surabaya, Indonesia. **Methods:** All SCADR patients at Dr. Soetomo Hospital, Surabaya, Indonesia in the period of January 2016 – June 2017 was evaluated. Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and exfoliative dermatitis cases were included in the study. **Results:** There were 24 patients in this study, consisted of 11 SJS cases, 1 TEN case, 2 SJS/TEN-overlap cases, 10 exfoliative dermatitis cases. The mean of latent period between drug intake and onset of symptoms was 15.8 days. The most common offending drug was mefenamic acid (20.9%), followed by cefadroxil and phenytoin (each 16.7%). Antibiotics was the highest frequent offending drug-groups (62.5%), followed by non-steroid anti-inflammatory drugs (NSAIDs). Prompt withdrawal of the offending drugs, systemic corticosteroid, and supported therapy were given to all patients, which gave good results in 21/24 patients (87.5%). **Conclusion:** Antibiotics were the most common offending drug-groups. SCADR might give high mortality rate, but early diagnosis, prompt withdrawal of the suspected drugs, closed monitoring to evaluate complications can improve the prognosis of SCADR.

**Key words:** clinicoepidemiology, severe CADR.

**ABSTRAK**

**Latar belakang:** Erupsi obat bervariasi dari reaksi ringan hingga berat. Penelitian mengenai kejadian erupsi obat berat terutama di rumah sakit umum masih sedikit. **Tujuan:** Mengevaluasi profil klinik dan epidemiologi erupsi obat berat. **Metode:** Seluruh pasien erupsi obat berat di Instalasi Rawat Inap Kesehatan Kulit dan Kelamin RSUD Dr. Soetomo Surabaya periode Januari 2016 – Juni 2017 dievaluasi. *Stevens-Johnson Syndrome* (SJS), *Toxic Epidermal Necrolysis* (TEN), *Acute Generalized Exanthematous Pustulosis* (AGEP), *Drug Reaction with Eosinophilia and Systemic Symptoms* (DRESS) dan dermatitis eksfoliatif dievaluasi pada penelitian ini. **Hasil:** Dua puluh empat pasien yang terdiri dari 11 kasus SJS, 1 kasus TEN, 2 kasus SJS/TEN-*overlap*, 10 kasus dermatitis eksfoliatif didapatkan pada penelitian ini. Rata-rata periode laten antara penggunaan obat dan onset gejala adalah 15,8 hari. Obat yang diduga sebagai penyebab terbanyak adalah asam mefenamat (20,9%), diikuti sefadroksil dan fenitoin (masing-masing 16,7%). Antibiotik merupakan kelompok obat yang diduga sebagai penyebab terbanyak (62,5%), diikuti oleh *non-steroid anti-inflammatory drugs* (NSAIDs). Penghentian obat yang diduga sebagai penyebab, kortikosteroid sistemik, dan terapi suportif diberikan pada semua pasien, dan memberikan hasil baik pada 21/24 pasien (87,5%). **Simpulan:** Antibiotik merupakan kelompok obat penyebab tersering pada erupsi obat berat pada penelitian ini. Erupsi obat berat dapat menyebabkan angka mortalitas yang tinggi, tetapi dengan penegakan diagnosis dini, penghentian obat penyebab, serta pengawasan ketat terhadap timbulnya komplikasi dapat meningkatkan prognosis.

**Kata kunci:** epidemiologi klinis, erupsi obat berat.

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## INTRODUCTION

Complication of drug therapy is the major cause of patient morbidity and may account for significant number of patient deaths. Drug eruption vary from mild reaction as transient erythema to severe and life-threatening form (defined as severe cutaneous adverse drug reaction or SCADR). SCADR is severe form of drug eruption, that might be fatal, need longer length

of stay at the hospital, cause persistent disability or life-threatening condition. SCADR might give high mortality rate (1-5%), especially in TEN cases (25-35%).[1,2]

As there were many new drugs nowadays, the pattern of drug eruption and the offending drugs also change. Drug eruptions usually are underreported and the clinical manifestation were similar to viral exanthemas or other disease. An early diagnosis making and avoiding the offending drugs are very important in the management of drug eruption.[1,2] This study was aimed to evaluate clinical and epidemiological profile of SCADR during 18 months period at Dermatology and Venereology Ward Dr. Soetomo Hospital Surabaya Indonesia retrospectively.

## METHODS

This study was a retrospective study, that evaluate secondary data from medical records of severe cutaneous adverse drug reaction (SCADR) patients admitted to Dermatology and Venereology Ward Dr. Soetomo Hospital, Surabaya, Indonesia during 18 months period (January 2016 - June 2017). All patients were evaluated clinically and epidemiologically. Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and exfoliative dermatitis cases were included in the study. The drug reaction patterns and the common offending drugs were identified. The ethical clearance of this study had been approved by Ethical Committe of Dr. Soetomo General Hospital Surabaya.

## RESULTS

During 18 months period, 35 of 305 (11.5%) patients admitted to Dermatology and Venereology Ward Dr. Soetomo Hospital Surabaya Indonesia, were drug eruption cases. Twenty-four patients from thirty five (68.6%) drug eruption cases admitted to the ward were severe form (SCADR). Of these 24, there were 11 SJS cases, 1 TEN case, 2 SJS/TEN overlap cases and 10 exfoliative dermatitis cases.

Female outnumbered males (the female to male ratio being 2.4:1). There was a female predominant in all types of SCADR. The most common age group in this study was 25-59 year-old (58.3%), with decline in prevalence of SCADR in those less than 14 year-old. The mean of age in this study was 40.5 year-old (Figure 1). Majority reaction pattern observed was SJS (11/24, 45.8%), followed by exfoliative dermatitis ( Figure 2).

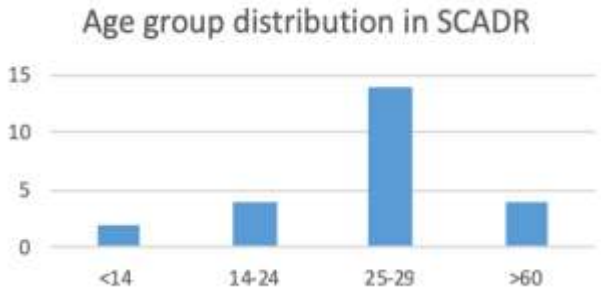


**Figure 1**. Age group distribution in Severe Cutaneous Adverse Drug Reaction (SCADR).

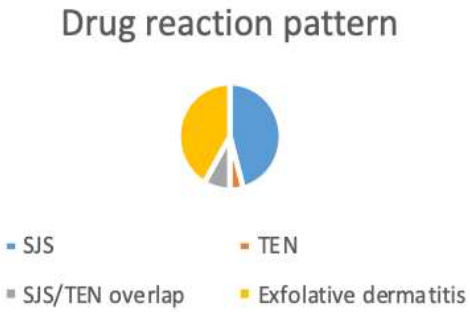


**Figure 2**. Drug reaction pattern. Explanation: SJS = Stevens-Johnson Syndrome; TEN = Toxic Epidermal Necrolysis.

The most common offending drug group in this study were antibiotics (15/24, 62.5%), followed by Non-Steroid Anti-Inflammatory Drug (NSAIDs) (41.7%) (Table 1). Mefenamic acid was the most common offending drug (5/24, 20.9%), followed by cefadroxil and phenytoin (each 16.7%) (Table 2).

**Table 1.** Offending drug-groups in Severe Cutaneous Adverse Drug Reaction (SCADR)

| Offending drug-group | Type of reaction | | | | Total |
|---|---|---|---|---|---|
| | SJS | TEN | SJS/TEN-overlap | Exfoliative dermatitis | |
| Antibiotics | 3 | 3 | 1 | 8 | 15 |
| NSAIDs | 6 | 0 | 1 | 3 | 10 |
| Anticonvulsants | 7 | 0 | 0 | 2 | 9 |
| Antigout | 0 | 1 | 0 | 0 | 1 |
| Antigastritis | 1 | 0 | 0 | 0 | 1 |
| Antidiabetic | 0 | 0 | 0 | 1 | 1 |
| Herbal medicine | 0 | 0 | 0 | 1 | 1 |

*Each patients may be caused by more than 1 offending drug-groups

Explanation: NSAIDs = non-steroid anti-inflammatory drug; SJS = Stevens-Johnson Syndrome; TEN = Toxic Epidermal Necrolysis.

**Table 2.** Offending drugs in Severe Cutaneous Adverse Drug Reaction (SCADR)

| Offending drugs | Number of patients |
|---|---|
| Clindamycin | 2 |
| Erythromycin | 1 |
| Ceftriaxone | 2 |
| Cefadroxil | 4 |
| Ciprofloxacin | 2 |
| Amoxycillin | 1 |
| Anti tuberculosis drugs | 1 |
| Multidrugs therapy for Hansen disease | 1 |
| Levofloxacin | 1 |
| Mefenamic acid | 5 |
| Metamizole | 1 |
| Paracetamol | 2 |
| Antalgin | 1 |
| Natrium diclofenac | 1 |
| Phenytoin | 4 |
| Clobazam | 3 |
| Carbamazepine | 2 |
| Ranitidine | 1 |
| Insulin | 1 |

*Each patients may be caused by more than 1 offending drugs

Explanation: SCADR = Severe Cutaneous Adverse Drug Reaction

**Table 3.** Profile of Severe Cutaneous Adverse Drug Reaction (SCADR) patients

| | SJS (n=11) | TEN (n= 1) | SJS/TEN- overlap (n=2) | Exfoliative dermatitis (n=10) |
|---|---|---|---|---|
| Mean of latent period between drug intake and onset of symptoms (range) | 13.5 days (1-45 days) | 1 day | 3.5 days (1-60 days) | 20.7 days (1-45 days) |
| Mean of age (range) | 27.8 year-old (8-67) | 67 | 55 year-old (54-56) | 49 year-old (24-75) |

Explanation: SJS = Stevens-Johnson Syndrome; TEN = Toxic Epidermal Necrolysis.

Latent period between the drug intake and the onset of symptoms varied from 1 day to 45 days in drug eruption (Table 5). With antibiotics, the time interval between the drug intake and the onset of symptoms was 1-7 days, whereas with NSAIDs was 1-10 days. Anticonvulsants produced eruption in 16-45 days after the drug intake. Nine of twenty-four patients (37.5%) got the eruption after the drug intake for an infectious disease (antibiotics or NSAIDs).

From history taking, none of patients in this study had history of CADR in a close family member. Two patients had history of previous CADR. Comorbidities noted in this study were hypertension (1 patient), diabetes mellitus (3 patients), post stroke (2 patients), tuberculosis infection (1 patient). Two patients had multiple comorbidities; 2 patient with diabetes mellitus and hypertension.

Prompt withdrawal of the culprit drugs were done to all patients. All patients were treated with systemic corticosteroid and supported therapy, based on patient's underlying diseases and condition. These management gave good results in 21/24 patients (87.5%), except in 3 patients. Average length of stay in the hospital was maximum for exfoliative dermatitis patients and ranged from 1-4 weeks. For SJS, TEN and SJS/TEN-overlap varied from 1-3 weeks.

The majority complication observed in this study was hypoalbumin (16.7%), followed by septicemia (8.3%), and pneumonia (4.2%). In this study, the mortality rate was 3/24 (12.5%) patients (1 SJS case, 1 TEN case, and 1 exfoliative dermatitis case).

## DISCUSSION

Adverse drug reaction (ADR) is defined as unpredictable response to drug administration in normal dose. ADR occured in 6.5% patients admitted to the hospital, with mortality rate 2%. Drug eruption was the most common form of ADR, which 2-7% of it was severe form (SCADR). The incidence of SCADR was range from 1.4-6 :1.000.000 people per year and became one of the common cause of patient death in the hospital.[1,3]

In this study, the incidence of drug eruption was 11.5% from all patients admitted to the ward, and 68.6% of it was severe form. SJS was the most common form of SCADR. Other studies also obtained similar results. Choon SE, et al (2012) showed that SJS was the most common form of SCADR in the study (110/362, 30.4%). A study in China also showed that the risk of SCADR was 0.03:1.000 patients (0.02:1.000 SJS cases, 0.01:1.000 exfoliative dermatitis, and DRESS cases). Analysis of the data revealed that most of the patients in this study were in 25-59 years age group, similar to other studies. This might correlating with increasing of drug use (multipharmacy) and potential for drug interaction, and drug alteration by the body. The decline after 60 years age group might be due to immunodeficiency associated with old age.[4-6]

The most common offending drug group in this study were antibiotics (62.5%), followed by NSAIDs and anticonvulsants. Other studies also showed similar results. One study found that the offending drugs in SCADR in the study were antibiotics (34.1%), followed by anticonvulsants (32.8%), and NSAIDs (21.5%). A study in China showed antibiotics was the most common offending drug, followed by antiepileptic drugs and Chinese herbal medicine.[5,7] In this study, mefenamic acid was the most common offending drug (5/24, 20.9%). Mefenamic acid is one of NSAIDs. NSAIDs were administered in many symptoms, such as pain, fever, or other inflammation condition, usually it was over the counter drugs (OTC). Many people were exposed to NSAIDs, so that it had high possibility to cause drug eruption. The reaction might be acute or delayed type reaction. Acute reaction consist of angioedema and urticaria, with pirazolone as the most common offending drug, followed by aspirin, paracetamol, ibuprofen, diclofenac, and naproxene. Delayed type reaction occured more than 24 hours after drug intake; may cause maculopapular eruption, fixed drug eruption, and bullous drug reaction (SJS, TEN, AGEP). On re-exposure to the same drug, all these reactions can develop within 24 hours.[7-10]

All drugs can produce any type of drug eruption in susceptible individuals, but some drugs are more likely to produce certain form, and this can be a clue regarding the likely causative drugs. Aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine), sulfonamide antibiotic, penicillin, cephalosporin, antituberculosis drugs, and allopurinol are more likely to produce SJS/TEN. Antibiotics, NSAIDs, dapsone, anticonvulsants are more likely induce exfoliative dermatitis.[1,4]

A recent evidence of drug eruption has been elucidated the association between Human Leukocyte Antigen (HLA) alleles and drug hypersensitivity association with specific drugs. These reactions were immunologically mediated and has furthered the understanding of their immunopathogenesis. Futhermore, these HLA associations also give promise that type B reaction (the unpredictable type of drug reaction) would be predictable and preventable in the future. Drugs causing SJS/TEN

overlap similar with those causing DRESS, with the common drug were NSAID, sulfa antibiotics, aromatic anticonvulsants, allopurinol, and antiretroviral. The clinical manifestation of TEN is the result of massive and widespread death of keratinocyte and mucosal cells. Previous study showed that Fas, Fas Ligand, and granzyme triggered this process, but more recent studies suggested that secretory granulysin mediated generalized keratinocyte apoptosis. Moreover, quantities of granulysin in blister appeared having correlation with the severity of SJS/TEN. It is likely that SJS/TEN is mediated by CD8+ T-cell class I HLA-restricted process, which recently showed the association of HLA Class I alleles with drug-associated SJS/TEN. For others, specific HLA association with drug eruptions have been described, but it seems that it cannot be generalized across different population or ethnicities. Also, association between drug hypersensitivity and single gene or HLA allele may not exist, or may not be generalizable across different populations and races. Another potential explanation for this may be that some drugs are metabolized to a reactive metabolite by genetically polymorphic enzyme that differs in race and population. For example, the association between HLA-B*1502 and SJS/TEN associated with carbamazepine in Han Chinese, HLA-B*5801 and SJS/TEN and DRESS associated with allopurinol.[11]

The mean of latent period between the drug intake and the onset of symptoms was 20.7 days in this study. With antibiotics, the time interval between the drug intake and the onset of symptoms was 1-7 days, whereas with NSAIDs 1-10 days, and anticonvulsants 16-45 days. Type of drug eruption in this study were SJS, TEN, SJS/TEN-overlap, and exfoliative dermatitis, which most mechanism were delayed type hypersensitivity. In other studies about drug eruption, showed that the mean of latent period between the drug intake and the onset of symptoms was 2-4 weeks. So that in history taking, the drugs administered in the period 2-4 weeks before the eruption should be listed and discontinued.[5,7,8]

Prolonged length of stay at the hospital was expected as all these patients had varying degrees of clinical manifestation. It could be the reason for development of septicemia in 3 patients (1 SJS case, 1 TEN case, and 1 exfoliative dermatitis case), that caused death. One patient who died was a 67 year-old woman, who suffered TEN after clindamycin, erythromycin, and ceftriaxone administration for her urinary tract infection and septicemia condition. She also had multiple comorbidities (hypertension and diabetes mellitus), and suffered from complication (hypoalbumin, hypoglycemia, and hyponatremia). The second patient was an 18 year-old girl, who suffered SJS after taking antalgin for her common cold. She also got active tuberculosis infection and hypochromic anemia, and also suffered from complication (hypoalbumin and septicemia). The third patient was a 51 year-old woman, who suffered exfoliative dermatitis after taking powdered drug from doctor because of pain, but she did not know the ingredient of the drug. She suffered from hypoalbumin and septicemia complication. One exfoliative dermatitis patient in this study developed pneumonia, but then improved, even the decrease of the length of stay at the hospital, might be due to closed monitoring and early intervention.[1,4]

Adverse drug reaction occured in 6.5% patients admitted to the hospital. Drug eruption or cutaneous adverse drug reaction was the most common form and 2-7% of it was severe form. In this study, SJS was the commonest type of SCADR (45.8%) followed by exfoliative dermatitis (41.7%). Antibiotics was the most common offending drug-groups in SCADR cases, and the mortality rate was 12.5%. SCADR might give high mortality rate. Early diagnosis, prompt withdrawal of the suspected drugs, closed monitoring to evaluate complications, and also performing drug patch test can improve the prognosis of drug eruption, especially in severe cases.

## REFERENCES

1. Grando LR, Schhmitt TA, Bakos RM. Severe cutaneous reactions to drugs in the setting of a general hospital. An Brass Dermatol 2014; 89(5): 758-62.
2. Shear NH, Knowles SR. Cutaneous reactions to drugs. In: Goldsmith AI, Katz S, Gilchrest A, Paller A, Leffel D, Wolff K, eds. Fitzpatrick Dermatology in General Medicine. 8thed. New York: McGraw Hill; 2012. P. 449-57.
3. Verma CR, Vasudevan LCB, Pragasam LCV. Severe cutaneous adverse drug reactions. Med J Armed Forces India 2013; 69: 375-83.
4. Sasidharanpillai S, Riyaz N, Khader A, Rajan U, Binitha MP, Sureshan DN. Severe cutaneous adverse drug reactions: a clinicoepidemiological study. Indian J Dermatol 2015; 60(1): 102.
5. Thong BY, Tan TC. Epidemiology and risk factors for drug allergy. Br J Clin Pharmacol 2011; 71 (5): 684-700.
6. Choon SE, Lai NM. An epidemiological and clinical analysis of cutaneous adverse drug reactions seen in a tertiary hospital in Johor, Malaysia. IJVDL 2012; 78(6): 734-9.

7. Nayak S, Acharjya B. Adverse cutaneous drug reaction. Indian J Dermatol 2008; 53(1): 2-8.
8. Borges MS, Foncesa FC, Hullet AC, Aveledo LG. Hypersensitivity reaction to NSAID: an update. Pharmaceuticals 2010; 3: 10-8.
9. Harr T, Rench LE. Toxic epidermal necrolysis and Stvens-Johnson syndrome. Orphanet J Rare D 2010; 5: 39-46.
10. Ho HHF. Diagnosis and management of Stevens-Johnson syndrome and Toxic Epidermal Necrolysis. Hong Kong Med J 2008; 13(10): 17-20.
11. Phillips EJ, Mallal SA. Pharmacogenetics of drug hypersensitivity. Pharmacogenomics 2010; 11(7): 973-87.