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Original article

# Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS): 11 years retrospective study in Thailand

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ALT, alanine aminotransferase; AKI, acute kidney injury; CKD, chronic kidney disease; DRESS, drug reaction with eosinophilia and systemic symptoms; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HHV-6, human herpesvirus 6; HLA-B, major histocompatibility complex, class I, B; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RegiSCAR, European Registry of Severe Cutaneous Adverse Reactions; WHO–UMC, World Health Organization–The Uppsala Monitoring Centre

ABSTRACT

*Background:* Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare but life-threatening adverse drug reaction. Several criteria have been established to aid the diagnosis. However, patients with DRESS remained underdiagnosis and undertreatment.
*Methods:* Medical records of hospitalized patients at the King Chulalongkorn Memorial Hospital from January 2004–December 2014 due to DRESS were enrolled retrospectively using RegiSCAR diagnostic criteria.
*Results:* A total of 52 patients were included. Thirty-seven patients (71.2%) were female. The four most common causative agents were phenytoin (23.1%), nevirapine (17.3%), allopurinol (15.4%), and cotrimoxazole (13.5%). The overall prevalence was 9.63 cases per 100,000 inpatients. Median onset time (IQR) was 16 (9–27) days. Allopurinol was associated with longer onset time than others ($p = 0.014$). Clinical presentation: skin rash 100%, fever 78.8%, and lymphadenopathy 50%. The majority (84.6%) had single internal organ involvement. The most common internal organ involvement was liver (94.2%). Allopurinol was associated with higher incidence of renal involvement ($p = 0.01$). Up to 60% of patients had eosinophilia. Allopurinol was associated with higher eosinophilia ($p = 0.003$). A half of patients received systemic corticosteroids. Two mortality cases were reported (omeprazole-fulminant hepatitis and phenytoin-nosocomial infection).
*Conclusions:* DRESS is associated with severe morbidity and mortality. Phenytoin, nevirapine, allopurinol, and cotrimoxazole were the major causes. Allopurinol-induced DRESS had the longest onset time, and was associated with higher eosinophilia and incidence of renal involvement. Raising awareness among both health care providers and public for early detection and withdrawal of the causative agent is critical to save life and reduce morbidity.


## Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare but severe adverse drug reaction characterized by fever, cutaneous eruption, and involvement of one or more internal organs. Although it was first introduced by Bocquet *et al.* in 1996,[1] the term DRESS is still inconsistent due to its variable clinical

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manifestations and inconsistent level of eosinophil, thus making the diagnosis challenging. Moreover, there are several nomenclatures for this syndrome such as drug hypersensitivity syndrome, drug-induced delayed multiorgan hypersensitivity syndrome, and drug-induced hypersensitivity syndrome, making diagnosis of DRESS more confusing.[2–4] In Asia, DRESS was reported to almost one tenth of adverse drug reaction cases, with a mortality rate ranged 3–10%.[5–8] Mortality cases were mainly caused by multiple organ failure and sepsis. Various medications have been described to be the cause of DRESS. Phenytoin and allopurinol were two most commonly reported culprit drugs.[5–8]

The objectives of this study are to evaluate and describe the causative agents, severity, and the clinical course of patients with DRESS hospitalized at an Asian tertiary care setting.

## Methods

This study is a descriptive retrospective study of hospitalized patients at the King Chulalongkorn Memorial Hospital between January 2004 and December 2014 due to DRESS. Using the electronic database of Faculty of Medicine, Chulalongkorn University, we were able to recruit the target patients. Because there is currently no ICD10 specifically used for DRESS, L27.0 (generalized skin eruption due to drugs and medicaments) and T88.7 (unspecified adverse effect of drug or medicament) were used. All medical records, including those whom DRESS were not the initial diagnosis, were then further reviewed to identify patients fulfilling the diagnostic criteria of DRESS.

The diagnostic criteria used in this study were purposed by European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR).[9] Hospitalization and reaction suspected to be drug related were mandatory for diagnosis. Also, 3 out of the following 7 criteria were needed to fulfill the diagnosis: acute skin rash, fever above 38 °C, enlarged lymph node at 2 or more sites, involved at least 1 internal organ, lymphocyte count above or below laboratory limits, eosinophil count above laboratory limits, and platelet count below laboratory limits. Patients who corresponded to the RegiSCAR criteria were then further evaluated using scoring system for classifying cases as definite, probable, possible, or no case. Only definite, probable, and possible cases were included for further analysis.

As for culprit drugs, a modification to that of WHO–UMC causality categories was applied to identify the culprit drug.[10] Classification of culprit drugs in this study were definite reaction (proven by challenge or provocative test), probable reaction (improving by withdrawing only the culprit drug or had taken only culprit drug before presentation), and possible reaction (improving by withdrawing multiple drugs, including the suspected culprit drug or had taken multiple medication but the culprit drug was suspected because of its incidence).

The statistical analyses used for evaluation of the significance of differences in this study were Mann–Whitney U Test for continuous variables and Chi-square for categorical variables. A value of $p < 0.05$ was regarded as significance.

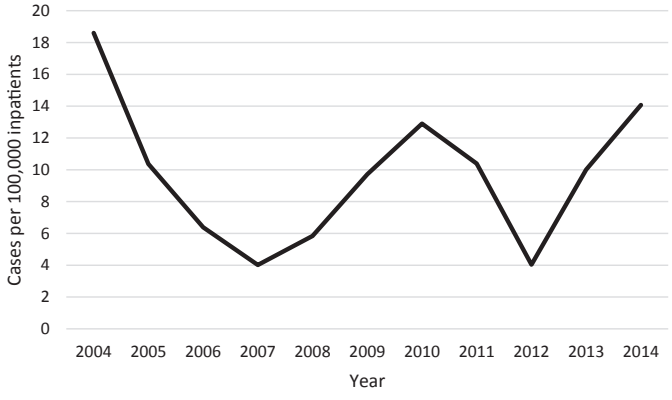



**Fig. 1.** Yearly prevalence of DRESS in the King Chulalongkorn Memorial Hospital, Bangkok, Thailand during 2004–2014.

## Results

Of 540,099 admissions to the King Chulalongkorn Memorial Hospital between January 2004 and December 2014, fifty-two patients were included. The yearly prevalence is shown in Figure 1. The overall prevalence during 11 years period was 9.63 cases per 100,000 inpatients. The highest prevalence was in 2004 (18.6 cases per 100,000 inpatients).

A total of 52 patients were included in this study. Using RegiSCAR scoring system, 28 patients were classified as possible case, 18 patients as probable case, and 6 patients as definite case. A summary of the demographic and baseline characteristics are shown in Table 1. There were 15 male and 37 female patients, giving a male to female ratio of 1:2.47. The age group ranged from 2 to 86 years (median age 33 years). Allopurinol-induced DRESS was associated with older age group ($p < 0.001$). The median onset time (IQR) was 16 (9–27) days. Allopurinol was associated with longer onset time, median (IQR) of 30 days (20.3–40.8) ($p = 0.014$). The period of hospitalization ranged from 2 to 54 days, with a median (IQR) of 7 (5–9) days.

Eight patients (15.4%) had previous history of drug allergy. All drugs were different from the culprit drug responsible for this hospitalization.

The most common causative drug was phenytoin (23.1%). Other common causes were nevirapine, allopurinol, and cotrimoxazole (17.3%, 15.4%, and 13.5%, respectively) (Fig. 2). Of noted, half of the causative drugs were anti-infectious agents.

The most common underlying disease was HIV infection (28.8%), all of whom had reported anti-infectious agents as the

**Table 1**
Demographic characteristics.

| | No. (%) |
|---|---|
| Sex (n, %) | |
| Female:Male | 37 (71.2):15 (28.8) |
| Median age (IQR) years | 33 (25.3–53.3) |
| Median hospital stay (IQR) days | 7 (5–9) |
| Median onset (IQR) days | 16 (9–27) |
| Initial diagnosis (n, %) | |
| Drug reaction with eosinophilia and systemic symptoms (DRESS) | 28 (53.8) |
| Drug-induced hypersensitivity syndrome (DIHS) | 14 (26.9) |
| Drug hypersensitivity | 6 (11.5) |
| Drug allergy | 4 (7.7) |
| Case classification according to RegiSCAR score | |
| Definite (score >5) | 6 (11.5) |
| Probable (score 4–5) | 18 (34.6) |
| Possible (score 2–3) | 28 (53.8) |
| History of drug allergy (n, %) | 8 (15.4) |
| Underlying disease (n, %) | 42 (80.8) |
| HIV | 15 (28.8) |
| Convulsion disorder | 12 (23.1) |
| Hypertension | 13 (25.0) |
| Dyslipidemia | 9 (17.3) |
| Diabetes mellitus | 8 (15.4) |
| Hyperuricemia | 8 (15.4) |
| Chronic kidney disease | 4 (7.7) |
| Others | 13 (25.0) |

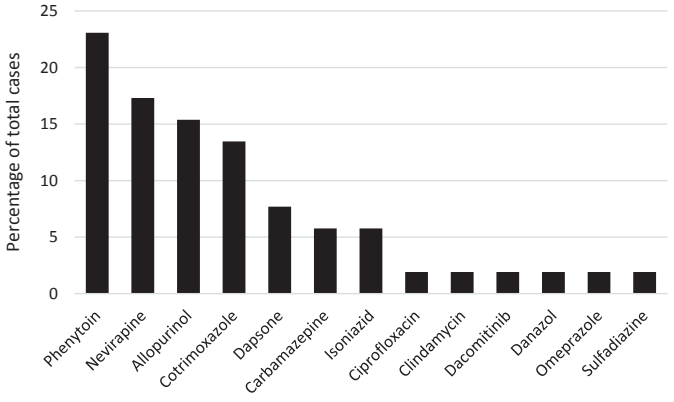



**Fig. 2.** Summary of culprit drugs of DRESS in this study.

culprit drugs. Table 2 shows a relationship between all anti-infectious agents reported to be culprit drugs and the underlying disease of HIV infection.

A summary of clinical characteristic is shown in Table 3. All patients presented with rash, almost all were maculopapular type (94.2%). Other common skin rashes included plaque, patch, and target lesions. Seven patients also reported to have either facial edema or periorbital edema. Conjunctival injection was reported in 4 patients. Fever, lymphadenopathy, and hepatomegaly were the other common clinical findings (78.8%, 50.0, and 34.6%, respectively). Majority of lymphadenopathy involved cervical lymph nodes. Gastrointestinal symptoms were also reported in 7 patients.

Forty-four patients (84.6%) had single internal organ involvement, while others had two or more internal organ involvements. Of 8 patients who had two organ internal organ involvements, 6 patients had a combination of liver and kidney involvement. Liver was the most common internal organ involved, accounted for 94.2%. Median level (IQR) of alanine aminotransferase (ALT) was 333 (215–690) IU/L. The kinetic of ALT level of the 4 most common causative drugs were shown in Figure 3. Nevirapine-induced DRESS was associated with significant increase of ALT level during the first 2 weeks of onset of symptoms compared to the others ($p = 0.005$). Eight patients (15.4%) had kidney involvement. All kidney involvement were acute kidney injury (AKI), with 2 of those reported to have AKI on-top chronic kidney disease (CKD). Allopurinol-induced DRESS was associated with higher incidence of renal involvement (62.5% versus 6.8% of allopurinol versus non-allopurinol, respectively, $p = 0.01$). Two patients had pneumonitis and one patient had splenomegaly.

Eosinophilia was reported in 30 patients (57.7%), with a median % eosinophil (IQR) of 18.1% (12.9–22.9) and a median absolute eosinophil count (IQR) of 1,482 (856.7–3,652.2) cells/μL. Both median % eosinophil and median absolute eosinophil were higher in patient whom allopurinol was the culprit drug ($p = 0.009$ and $p = 0.003$, respectively) (Table 4). Fourteen patients (26.9%) had atypical lymphocyte, with a median % atypical lymphocyte (IQR) of 10% (6–20.5). Thirteen patients (25%) had thrombocytopenia, with a median platelet count (IQR) of 84,000 (53,000–111,000) cells/μL. Lymphopenia was also reported in approximately a half the patients (51.9%). Blood test for human herpesvirus 6 (HHV-6) was performed in 6 patients. The results were positive for serum IgG antibody and negative for serum IgM antibody in 4 patients. No further quantitative test was done. The results for 2 remaining patients were unavailable.

The culprit drug was discontinued in every patient. Up to 85%, the culprit drug was discontinued in the first day of admission. The longest duration until discontinuation was 11 days (phenytoin was the culprit drug, this case was fortunately survived). Systemic corticosteroid, either intravenous dexamethasone or oral prednisolone, was administered to 30 patients (57.7%). Forty-nine patients (94.2%) received antihistamine, either chlorpheniramine or hydroxyzine (Table 5). However, when evaluated only in those who initial diagnosis were DRESS, systemic corticosteroid was administered in 23 out of 28 patients (82.1% versus 29.2% of whom initial diagnosis were DRESS versus other initial diagnosis, respectively, $p < 0.001$). There was no different in lag time of systemic corticosteroid administration between the 2 groups.

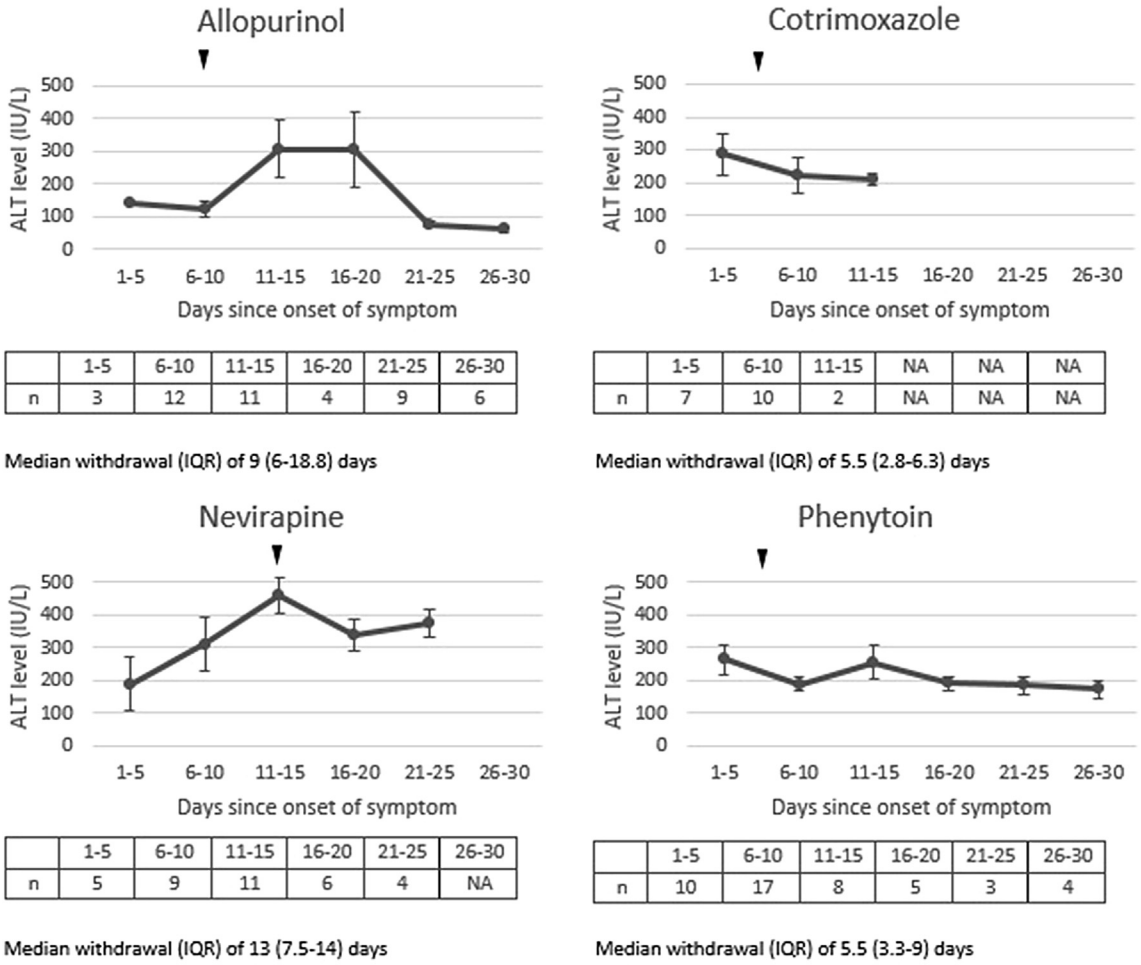
Two patients died during admission. One died from DRESS-related fulminant liver failure and the other was from nosocomial infection. The culprit drugs were omeprazole and phenytoin, respectively.

**Table 2**
Relationship between all anti-infectious agents reported to be culprit drugs and underlying disease of HIV infection. Half the culprit drugs were anti-infectious agents. All patients with underlying HIV infection had anti-infectious agents as their culprit drugs.

| Culprit drugs | Overall n = 26 | Known HIV infection | |
|---|---|---|---|
| | | Yes n = 15 | No n = 11 |
| Ciprofloxacin | 1 | – | 1 |
| Clindamycin | 1 | – | 1 |
| Cotrimoxazole | 7 | 4 | 3 |
| Dapsone | 4 | – | 4 |
| Isoniazid | 3 | 1 | 2 |
| Nevirapine | 9 | 9 | – |
| Sulfadiazine | 1 | 1 | – |

**Table 3**
Clinical characteristics.

| | No. (%) |
|---|---|
| Fever | 41 (78.8) |
| Lymphadenopathy | 26 (50.0) |
| Skin rash | 52 (100) |
| Extent of rash > 50% | 23 (44.2) |
| Maculopapular rash | 49 (94.2) |
| Bullous | 1 (1.9) |
| Wheal & flare | 1 (1.9) |
| Plaque | 2 (3.8) |
| Patch | 2 (3.8) |
| Target lesion | 2 (3.8) |
| Facial edema | 4 (7.7) |
| Periorbital edema | 3 (5.8) |
| Conjunctival injection | 4 (7.7) |
| Abdominal pain | 3 (5.8) |
| Diarrhea | 4 (7.7) |
| Hepatomegaly | 18 (34.6) |
| Splenomegaly | 1 (1.9) |
| Internal organ involvement | |
| 1 organ involved | 44 (84.6) |
| 2 or more organs involved | 8 (15.4) |
| Liver | 49 (94.2) |
| Median alanine aminotransferase level IU/L (IQR) | 333 (215–690) |
| Kidney | 8 (15.4) |
| Lung | 2 (3.8) |
| Other | 1 (1.9) |
| Hematologic abnormalities | |
| Eosinophilia | 30 (57.7) |
| Median % Eosinophil (IQR) | 18.1 (12.9–22.9) |
| Median absolute eosinophil/μL (IQR) | 1,482 (856.7–3,652.2) |
| Atypical lymphocyte | 14 (26.9) |
| Median % atypical lymphocyte (IQR) | 10 (6–20.5) |
| Lymphocytosis | 14 (26.9) |
| Median lymphocyte count/μL (IQR) | 9,154 (6,024–15,594) |
| Lymphopenia | 27 (51.9) |
| Median lymphocyte count/μL (IQR) | 680 (456–1,058) |
| Thrombocytopenia | 13 (25) |
| Median platelet count/μL (IQR) | 84,000 (53,000–111,000) |




| | 1-5 | 6-10 | 11-15 | 16-20 | 21-25 | 26-30 |
|---|---|---|---|---|---|---|
| n | 3 | 12 | 11 | 4 | 9 | 6 |

Median withdrawal (IQR) of 9 (6-18.8) days

| | 1-5 | 6-10 | 11-15 | NA | NA | NA |
|---|---|---|---|---|---|---|
| n | 7 | 10 | 2 | NA | NA | NA |

Median withdrawal (IQR) of 5.5 (2.8-6.3) days

| | 1-5 | 6-10 | 11-15 | 16-20 | 21-25 | 26-30 |
|---|---|---|---|---|---|---|
| n | 5 | 9 | 11 | 6 | 4 | NA |

Median withdrawal (IQR) of 13 (7.5-14) days

| | 1-5 | 6-10 | 11-15 | 16-20 | 21-25 | 26-30 |
|---|---|---|---|---|---|---|
| n | 10 | 17 | 8 | 5 | 3 | 4 |

Median withdrawal (IQR) of 5.5 (3.3-9) days

**Fig. 3.** The kinetic change of mean with standard error (SE) of ALT level since the onset of DRESS by the 4 most common culprit drugs. ▼, the median day of culprit drug withdrawal since onset of symptoms. NA, not available. Nevirapine was associated with significant increase of ALT level during the first 2 weeks of onset of symptoms compared to the others ($p = 0.005$).

## Discussion

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare but severe adverse drug reaction, with broad clinical features. The estimated incidence of DRESS ranges from 1 in 1,000 to 1 in 10,000 drug exposures. A recent study in Europe reported an overall prevalence of 37.6 cases per 100,000 inpatients.[11] Multiple factors have been described to associate with DRESS

**Table 4**
Comparison between 4 most common culprit drugs and others.

| Features | Allopurinol n = 8 | *p* value† | Cotrimoxazole n = 7 | *p* value‡ | Nevirapine n = 9 | *p* value§ | Phenytoin n = 12 | *p* value¶ |
|---|---|---|---|---|---|---|---|---|
| Age, median (IQR), y | 75 (56.5–78.8) | <0.001* | 33 (21–39) | 0.528 | 30 (26.5–41.5) | 0.537 | 34.5 (27.5–45) | 0.948 |
| Hospitalization, median (IQR), d | 6 (5.3–15.3) | 0.813 | 7 (5–7) | 0.545 | 5 (3–9.5) | 0.146 | 10 (5.3–13) | 0.072 |
| Onset, median (IQR), d | 30 (20.3–40.8) | 0.014* | 21 (10–24) | 0.733 | 14 (5.5–14.5) | 0.064 | 16 (8.5–29.5) | 0.991 |
| Median days from onset of symptom to culprit drug withdrawal (IQR) | 9 (6–18.8) | 0.195 | 5.5 (2.8–6.3) | 0.127 | 13 (7.5–14) | 0.031* | 5.5 (3.3–9) | 0.192 |
| %Eosinophil, median (IQR) | 21.4 (14.4–32) | 0.009* | 8 (5.5–19.7) | 0.599 | 8.5 (2–14.5) | 0.282 | 15.2 (6.4–20) | 0.35 |
| Absolute eosinophil count, median (IQR), cells/μL | 3,192.4 (1,117.9–7,093.1) | 0.003* | 960 (431.2–1,702.1) | 0.511 | 243.5 (84.8–863.2) | 0.053 | 501.1 (192.6–2,920.2) | 0.745 |
| ALT, median (IQR), IU/L | 141 (109.5–748.3) | 0.108 | 332 (271) | 0.399 | 510 (346.5–717.5) | 0.304 | 284.5 (217–386.5) | 0.263 |
| Eosinophilia, Y (%) | 7 (87.5) | 0.12 | 5 (71.4) | 0.69 | 3 (33.3) | 0.14 | 7 (58.3) | 0.61 |
| Renal involvement, Y (%) | 5 (62.5) | 0.01* | 1 (14.3) | 0.71 | 1 (11.1) | 0.58 | 1 (8.3) | 0.66 |

ALT, Alanine aminotransferase; d, day; y, year; Y, yes.
*Statistically significant, when $p < 0.05$.
† Allopurinol group vs others.
‡ Cotrimoxazole group vs others.
§ Nevirapine group vs others.
¶ Phenytoin group vs others.

**Table 5**
Treatment received during hospitalization.

| | Overall n = 52 | Initial diagnosis DRESS n = 28 | Initial diagnosis not DRESS n = 24 | *p* value[†] |
|---|---|---|---|---|
| Systemic corticosteroid (%) | 30 (57.7) | 23 (82.1) | 7 (29.2) | <0.001* |
| Antihistamine (%) | 49 (94.2) | 26 (92.9) | 23 (95.8) | >0.999 |
| Topical corticosteroid (%) | 22 (42.3) | 14 (50) | 8 (33.3) | 0.225 |

*Statistically significant, when $p < 0.05$.
† Initial diagnosis DRESS vs Initial diagnosis not DRESS.

development such as defect of drug detoxification, human leukocyte antigen-related gene, and HHV-6 reactivation.[12,13] HHV-6 has been defined as a potential contributor to DRESS development.[14,15]

Uneven yearly prevalence of DRESS is seen in this study (Fig. 1). During 11 years period, there were some trends regarding the culprit drugs. The number of nevirapine-induced DRESS patients contributed to approximately 50% of DRESS cases during 2004 and 2005. Interestingly, nevirapine was the second most common culprit drugs in our study (17.3%) (Fig. 2). The result is uncommon compared to previous reported worldwide (5%).[16] Such finding could be explained by higher prevalence of underlying HIV infection in our study and more frequent prescription of nevirapine in Thailand in those years.[17] Before 2010, nevirapine was the only preferred NNRTI in HAART in Thailand. The number of nevirapine-induced DRESS cases had declined since 2005, until the last case reported in 2010, the same year when the Thailand's national guideline for antiretroviral therapy recommended efavirenz as an additional preferred NNRTI to nevirapine.[18]

The youngest patient in our study was a 2 years old girl diagnosed with carbamazepine-induced DRESS. Clinical presentations were high-grade fever, rash, lymphadenopathy, eosinophilia, and liver involvement. The onset time was 21 days and the patient stayed at the hospital for 5 days, which were both shorter than a case reported by EL omairi *et al.* on carbamazepine-induced DRESS in a 6 years old boy patient (4 weeks and 2 weeks, respectively).[19] On discharged, levetiracetam was given as a substitute with no subsequent adverse reaction reported. There are few reports of DRESS in children; and to our knowledge, our patient was among the youngest patients diagnosed with DRESS.

Aromatic anticonvulsant was responsible for 28% of all cases in our study. The most common culprit drug in our study was phenytoin (23.1%) (Fig. 2). The finding is similar to other studies which reported phenytoin and aromatic anticonvulsant to be the most common culprit drugs.[6,7,20,21] Notably, cross-reactivity is well documented among aromatic anticonvulsant,[12] thus avoidance of re-expose to such medication should not be missed. There was no history of potential aromatic cross-reactivity case in this study. Of all 12 patients who was diagnosed phenytoin-induced DRESS, phenytoin was switch to levetiracetam or valproic acid.

The third most common culprit drug in our study was allopurinol (15.4%) (Fig. 2). The result is similar to some earlier reports.[7,21] The finding can be described by high prevalence of HLA-B*5801 in Thai population. HLA-B*5801 has known to be closely associated with allopurinol-induced SCARs. Thus, recommendation of HLA-B*5801 screening before initiating allopurinol has been purposed as a risk management in select patient subpopulations with elevated risk, including Thai descent.[22,23] Another reason contributed to such finding is allopurinol can be bought as an over-the-counter drug in Thailand, thus the patients might not be aware of its potential side effects. Allopurinol was also associated with DRESS in older age group ($p < 0.001$). Higher accumulation of oxypurinol, an active metabolite of allopurinol, in geriatric patients resulted from declined renal function may be contributed to such finding.[24,25] In contrast to nevirapine, allopurinol-induced DRESS was first reported later in 2009 and increased during 2013 and 2014. The reason is unclear.

Half of the culprit drugs in our study were anti-infectious agents (Table 2). Fifteen of those had underlying HIV infection (Table 1). Therefore, the finding of high percentage of anti-infectious agent as the cause for DRESS in this study could be due to high proportion of patients with underlying HIV infection in our study.[5,7]

The median onset time, Table 1 and 4, in our study was comparable to the 22 days observed in the RegiSCAR study.[21] Similar to previous reports, allopurinol-induced DRESS was associated with longer onset time ($p = 0.014$).[7] Patients with allopurinol-induced DRESS had a median onset of 30 days, which is comparable to 3 weeks reported in a large systemic review of allopurinol hypersensitivity.[26]

All patients presented with rash (Table 3). Maculopapular rash was the most common feature (94.2%). Six patients have more than one feature of rashes. The histopathological feature of DRESS is poorly characterized. Presence of superficial perivascular lymphocytic infiltrate, extravasation of erythrocytes, necrotic keratinocytes, and, less frequently, dermal eosinophils were some of the patterns reported.[27] In our study, skin biopsy was done in 4 patients which showed perivascular lymphocytic infiltration, similar to previous reports.[5,7,28]

Proportion of patients with liver involvement, Table 3 and Figure 3, were similar to other reports from Asia, but were much higher compared to result from European studies.[5,21,29,30] There was no significant difference between the levels of ALT of each culprit drugs. However, because we were able to record and analyze the kinetics of the ALT level in 4 most common culprit drugs, we found a significant difference in kinetic change of ALT level in patients with nevirapine-induced DRESS during the first 2 weeks of onset of symptoms compared to the other 3 culprit drugs ($p = 0.005$). The longer period between onset of symptom and withdrawal of culprit drug could be the factor contributed to such result ($p = 0.031$). Also, the finding could be described by high prevalence of HLA*B35 in Thai population, which associated with nevirapine-induced hepatotoxicity.[31,32] Closed monitoring of transaminase during the first 12 week of nevirapine-containing has been recommended.[33] All patients with nevirapine-induced DRESS did not received systemic corticosteroid, thus the role of systemic corticosteroid towards nevirapine-induced hepatotoxicity is inconclusive in this study. However, the result suggests that withdrawal of nevirapine should rapidly prevent further elevation of abnormal ALT level.

The proportion of patients with renal involvement was similar to previous reports (16–53%).[7,21,34] Five out of eight patients who had renal involvement were caused by allopurinol, which represents 62.5% of patients whom allopurinol was the culprit drug (Table 4). The similar ratio of allopurinol-induced DRESS patients who have to those who don't have renal involvement was also reported (68.4%).[5]

Previous studies from both Asia and Europe showed varied number of patients with eosinophilia, ranging from 48 to 95%.[7,21,34] Despite dissociation between culprit drugs and presentation with eosinophilia, allopurinol was associated with significant higher eosinophil level compared to other culprit drugs ($p = 0.003$).

Withdrawal of suspected agent is the most important step in management of DRESS. Culprit drug was withdrawn in every patients in our study, with 84.6% had their culprit drug withdrawn within the first day of hospitalization. Systemic corticosteroid has been described as the treatment of choice. In our study, systemic corticosteroid was administered in 57.7% of patients. However, the number increased to 82.1% when considering only those who were initially diagnosed with DRESS. Neither the differences in median

time of resolution period (12.5 versus 14.5 days, $p = 0.191$) nor mortality outcome (1 versus 1 case, $p = 0.438$) between conservative treatment (i.e. without the use of systemic corticosteroid) and systemic corticosteroid were found in our study.

Two mortality cases were reported in our study. The first case was from fulminant liver failure due to omeprazole-induced DRESS. Proton-pump inhibitors (PPI) have been reported to cause cutaneous reactions frequently, but usually mild in intensity. Only one report of PPI-induced DRESS from Caboni *et al.* resulted from esomeprazole.[35] However, to our knowledge, mortality due to PPI-induced DRESS has not been reported before. Omeprazole was withdrawn in the third day of hospitalization along with administration of systemic corticosteroid. The second case, which died due to nosocomial infection, had her culprit drug (phenytoin) withdrawn in the first day of hospitalization. However, systemic corticosteroid was not administered because of possible concurrent infection. Unlike a previous study done in Taiwan which reported pronounced eosinophilia in mortality cases compared to non-mortality cases, eosinophilia was not significantly different to non-mortality cases ($p = 0.137$).

Study limitations include a retrospective study and small number of subjects. Despite small number of subjects, we began to see some unique clinical features between each drug. To confirm and provide more useful clinical information for early detection and improve the outcome of severe cutaneous adverse reactions including DRESS is underway under The Registry of Severe Cutaneous Adverse Reactions in Thailand (ThaiSCAR).

In conclusion, phenytoin, nevirapine, allopurinol, and cotrimoxazole are the major causes of DRESS. Allopurinol-induced DRESS has the longest onset time also associated with higher eosinophil level and higher incidence of renal involvement. The mortality rate in this study was 4%. Thus, raising awareness among both health care providers and public for early detection and withdrawal of the suspected agent is the principal step in management of DRESS.

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*Conflict of interest*

The authors have no conflict of interest to declare.

*Authors' contributions*

AH contributed to data collection, implementation of the study, interpretation of the data, writing the manuscript, and performed statistical analysis. TR contributed to study design, interpretation of the data and performed statistical analysis. JK, PR, and MP contributed to interpretation of the data and reviewing the manuscript. KR contributed to study design, implementation of the study, interpretation of the data, and reviewing the manuscript. All authors read and approved the final manuscript.

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