A Five-Year Review of Adverse Cutaneous Drug Reaction in a Tertiary Care Hospital in Yogyakarta, Indonesia

Dyah Ayu Mira Oktarina, Maria Sophiati, Erinda Maharani Rambu Moha, Fajar Waskito, Hardyanto Soebono

Department of Dermatology and Venereology, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/Dr Sardjito Hospital, Yogyakarta, Indonesia

ABSTRACT

Background: The prevalence of adverse drug reactions is likely to increase, and it is associated with increased usage of various drugs. Adverse Cutaneous Drug Reaction (ACDR) is the most frequent adverse drug reaction (30–45%). In Indonesia, the study on the prevalence of ACDR is still limited. **Purpose**: This study investigated the prevalence, clinical features, causative agents, and mortality rate of ACDR with a type-IV hypersensitivity reaction among patients attending the Department of Dermatology and Venereology in Dr. Sardjito Hospital, Yogyakarta. **Methods**: This retrospective study was conducted examining medical records undertaken for five years (2011–2015). Of 68,375 patients medicated in the Department of Dermatology and Venereology, 397 patients were diagnosed as ACDR with a type-IV hypersensitivity reaction. Detailed history, including age, sex, past history, and family history of drug reaction taken by the patient, were obtained. Patch testing was done wherever feasible. **Result**: Of 68,375 patients, 397 patients were included in ACDR with type-IV hypersensitivity (0.58%), giving a 5% of mortality rate. The mean age of the patients was 40.42 years (±16.30; range 18 to 89 years). The female to male ratio was 1.1: 1. The Maculopapular rash was the most common ACDR manifestation (50.88%), followed by Stevens-Johnson Syndrome (13.85%), Fixed Drug Eruption (12.85%), and Drug Reaction with Eosinophilia and Systemic Symptoms (10.08%).The most common causative agents were beta-lactam (16.55%), NSAIDs (12.18%), and acetaminophen (8.62%). **Conclusion**: Prescription of those drugs should be considered carefully so the incidence of ACDR can be reduced.

Keywords: drug eruptions, hypersensitivity, maculopapular exanthema rash, beta lactam.

Correspondence: Dyah Ayu Mira Oktarina, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada / Dr Sardjito Hospital, Yogyakarta, Indonesia. Email address: d.oktarina@ugm.ac.id, Tel: +6274560700.

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BACKGROUND

Adverse cutaneous drug reaction (ACDR) is an unpleasant and unanticipated side effect of a medicine on cutaneous that occurs at levels that are widely used in the general population.[1] Recently, the number of adverse drug reactions is likely to increase, associated with higher life expectancy and increasing access to health services for therapy using various drugs.[2] Adverse drug reaction occupies the fifth position of deadly diseases. About 30–45% of adverse drug reaction involves the skin.[3]

Generally, ACDR is classified into two groups: predictable-drug or non-immunologic reaction (Type-A reaction) and unpredictable-drug or immunologic reaction (Type-B reaction). Type-B reaction is caused by immune alteration that results in skin manifestations. There are four hypersensitivity reactions based on Coombs & Gells, consist of type-I hypersensitivity (Ig-E mediated), type-II hypersensitivity (cytotoxic reaction), type-III hypersensitivity (immune complex-mediated), and type-IV hypersensitivity (delayed-type).[4] Type-IV hypersensitivity reaction is mediated by T-lymphocyte and manifests as Maculopapular rash (MPR), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Fixed Drug Eruption (FDE), erythroderma, and Acute Generalized Exanthematous Pustulosis (AGEP).[2] Some researchers find that Maculopapular rash is the most common form of skin drug eruption, whereas others also state that FDR is the most frequent manifestation of ACDR.[5]

Unfortunately, the study of ACDR in Indonesia is limited. This study investigated the prevalence, clinical features, causative agents, and mortality rate of ACDR with type-IV hypersensitivity among patients in the Department of Dermatology and Venereology in Dr. Sardjito Hospital in Yogyakarta, ranged from 2011–2015.

METHODS

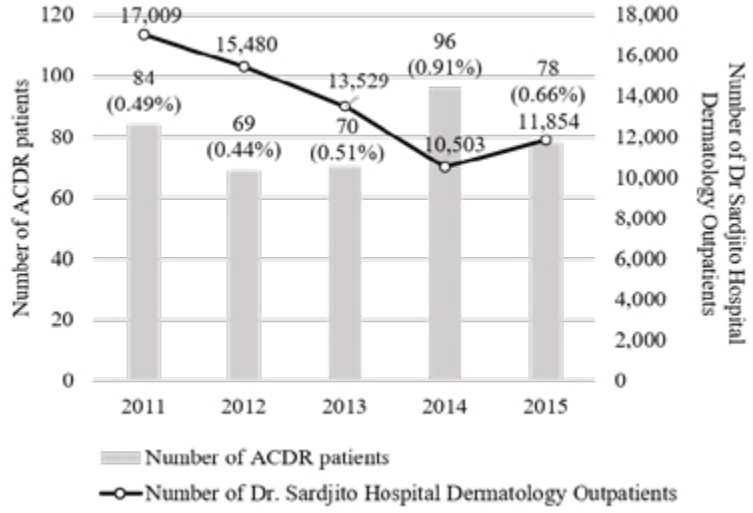
This retrospective observational study was undertaken for five years (2011–2015) by recording various medical records in the Department of Dermatology and Venereology in Dr. Sardjito Hospital in Yogyakarta. Detailed history, including age, sex, history, and family history of drug reaction taken by the patient, were recorded. Patch testing was done wherever feasible. Sample used in study were medical records from patient suffering from skin drug-eruption that fulfilled inclusion criteria: diagnosed as ACDR with type-IV hypersensitivity in the Department of Dermatology and Venereology in Dr. Sardjito Hospital, age ≥ 18 years old, and have complete data, include causative agents, clinical features, age, sex, and history of medication allergy. Patients with incomplete data were excluded from the study. Moreover, data analyzed were prevalence, clinical features, causative agents, and mortality rate of ACDR with type-IV hypersensitivity.

Ethical approval for this study project was obtained from the Ethical Committee of Research, Faculty of Medicine, Public Health, and Nursing University of Gadjah Mada, Dr. Sardjito Hospital, Yogyakarta, Indonesia, with certificate number: KE/FK/924/EC.

RESULT

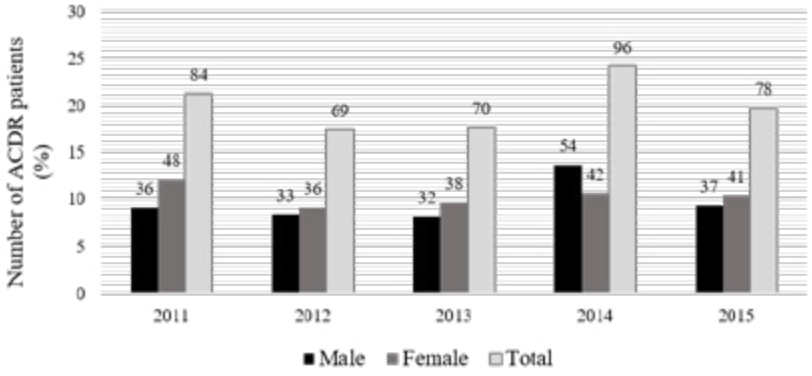
Throughout 2011–2015, there were 68,375 patients treated at the Department of Dermatology and Venereology of Dr. Sardjito Hospital, and 397 of them were categorized into ACDR with type-IV hypersensitivity, showing total prevalence of 0.58% (Figure 1). The diagnosis establishment was made by medical history and physical examination in 349 patients (87.9%), and the others were established by patch test (12.1%).

Three hundred and ninety-seven patients, 205 were females, and 192 were males (Figure 2). The female to male ratiowas 1.1: 1. The mean age of the patients was 40.42 ± 16.30 years. The age range of patients was 18 months to 89 years. Most cases of ACDR with type-IV hypersensitivity were observed in middle-adulthood (ranged from 35–60 years old), either in males or females (Figure 3).



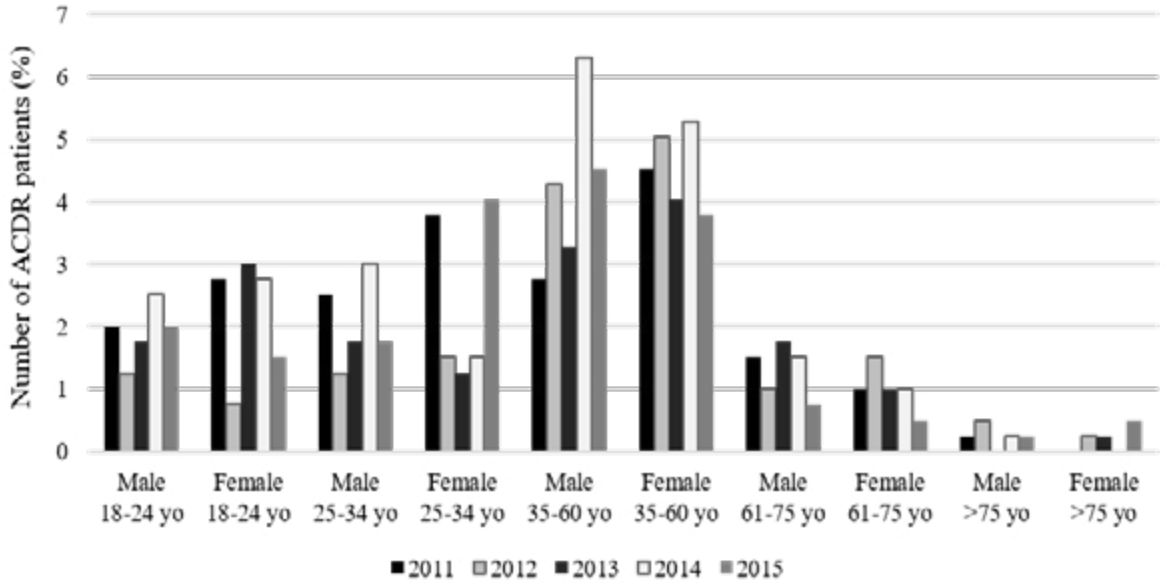
ACDR: Adverse Cutaneous Drug Reaction

Figure 1. Prevalence of Adverse Cutaneous Drug Reaction (ACDR) with a type-IV hypersensitivity in Dr. Sardjito General Hospital, 2011-2015.



ACDR: Adverse Cutaneous Drug Reaction

Figure 2. Total of Adverse Cutaneous Drug Reaction (ACDR) with type-IV hypersensitivity, comparison between male and female patients.



ACDR: Adverse Cutaneous Drug Reaction

Figure 3. Grouping of Adverse Cutaneous Drug Reaction (ACDR) patients based on age, between male and female patients.

Table 1. Causative agents of Adverse Cutaneous Drug Reaction (ACDR) and clinical manifestations

Drug classes	Percentage (%)	Common drugs implicated	Frequent clinical features (%)
Beta-lactam	16.55	Cefadroxil, Amoxicillin, Cefixime, Penicillin, Ceftriaxone	MPR (46.28%), DRESS (21.49%)
NSAID	12.18	Mefenamic Acid, Diclofenac, Metamizole, Meloxicam, Ibuprofen, Ketoprofen	MPR (38.20%), FDE (22.47%)
Acetaminophen	8.62	-	MPR (42.86%), FDE (20.64%)
ARV	6.98	-	MPR (74.51%)
Anticonvulsant	6.29	Carbamazepine, Phenytoin	SJS (36.96 %), MPR (23.91%), SJS-TEN (15.22%), TEN (4.35%)
Antituberculous drugs	5.88	-	MPR (69.77%), DRESS (16.28%)
Cotrimoxazole	4.51	-	MPR (57.58%), SJS (21.21%)
Quinolone	3.83	Ciprofloxacin, Levofloxacin	MPR (53.57%), DRESS (17.86%)
Other antibiotics	3.69	Metronidazole, Clindamycin, Azithromycin, Doxycycline	MPR (55.56%), SJS (29.63%)
ACE-i & ARB	2.60	Captopril, Valsartan, Irbesartan	MPR (47.37%), SJS (21.05%)
Allopurinol	2.33	-	SJS (47.06%), MPR (29.41%), SJS-TEN (11.77%)
Antihistamine	2.05	Chlorpheniramine Maleate, Ranitidine, Cetirizine	MPR (53.33%), SJS (20.00%)
Chemotherapy agents	1.92	Docetaxel, Bleomycin, Dacarbazine, Doxorubicin, Capecitabine, Carboplatin, Lapatinib, Leukokine, Methotrexate, Mitomycin, Nilotinib, Paclitaxel, Vinblastine	MPR (78.57%), FDE (14.29%)
CCB	1.50	Amlodipine	MPR (72.72%)
Diuretic	1.50	Furosemide	MPR (60.00%)

NSAID: Non-steroidal Anti-inflammatory Drugs, ARV: Antiretroviral, ACE-i: Angiotensin Converting Enzyme Inhibitor, ARB: Angiotensin Receptor Blocker, CCB: Calcium Channel Blocker, MPR: Maculopapular rash, DRESS: Drug Reaction with Eosinophiliaand Systemic Symptoms, FDE: Fixed Drug Eruption, SJS: Steven-Johnson Syndrome, TEN: Toxic Epidermal Necrolysis

Table 2. Distribution of most common drugs in each Adverse Cutaneous Drug Reaction (ACDR) with type-IV hypersensitivity

Clinical Features	Total Cases n (%)	Common drugs implicated
MPR	202 (50.88)	Beta-lactam (15.56%), ARV (10.56%), NSAID (9.44%)
SJS	55 (13.85)	Anticonvulsant (14.5%)
FDE	51 (12.85)	NSAID (27.03%), Acetaminophen (17.57%)
DRESS	40 (10.01)	Beta-lactam (32.91%), NSAID (18.19%)
Erythroderma	22 (5.54)	Beta-lactam (35.14%)
SJS-TEN	15 (3.78)	Anticonvulsant (19.44%)
AGEP	8 (2.02)	Beta-lactam (26.67%)
TEN	4 (1.01)	Anticonvulsant (22.22%)

MPR: Maculopapular rash, SJS: Steven-Johnson Syndrome, TEN: Toxic Epidermal Necrolysis, FDE: Fixed Drug Eruption, DRESS: Drug Reaction with Eosinophiliaand Systemic Symptoms, ARV: Antiretroviral, NSAID: Non-steroidal Anti-inflammatory Drugs

From 397 patients, 20 patients (5%) passed away due to ACDR with hypersensitivity reaction type IV, consist of SJS (9), SJS-TEN (4), TEN (1), FDE (3), MPR (1), and DRESS (2). The most common cause of drug reaction in dead patients were beta-lactam antibiotics (7), NSAID (4), and diuretics (3).

In this study, causative agents were classified into different drug classes. There were 731 drugs suspected as causative agents of ACDR with type-IV hypersensitivity; 80.43% drugs shown in table 2, other 19.56% drugs were causativeagents in a small cases; sulfonamide (1.37%), corticosteroid (1.23%), antianxiety and antidepressant agents (0.96%), antifungal (0.96%), anti-hyperlipidemia (0.96%), antiplatelet (0.96%), anti-psychotic (0.96%), mucolytic (0.96%), opiates (0.96%), antioxidant (0.68%), PPI (Proton Pump Inhibitor) (0.68%), herbal (0.68%), anti-diabetic (0.55%), anti-leprosy (0.55%), decongestant (0.55%), β-blocker (0.55%), antacid (0.41%), bronchodilator (0.41%), anti-diarrhea (0.41%), amiodarone (0.27%), anti-emetic (0.27%), propylthiouracil (0.27%), antitussive (0.27%), folic acid (0.27%), pipemidic acid (0.27%), tranexamic acid (0.27%), ursodeoxycholic acid (0.27%), expectorant (0.27%), hepatoprotector (0.27%), immune-modulator (0.27%), potassium aspartate (0.27%), biology agent (0.14%), alpha agonist (0.14%), anti-spasmodic (0.14%), acyclovir (0.14%), glycerin (0.14%), potassium chloride (0.14%), calcium lactat (0.14%), sodium bicarbonate (0.14%), piracetam (0.14%), citicoline (0.14%), and vitamin K (0.14%).

DISCUSSION

The prevalence of Adverse Cutaneous Drug Reaction (ACDR) with type-IV hypersensitivity was 0.58%. A study by Borch et al. in Odense University Hospital in Denmark showed the prevalence rate of ACDR was 1.38%.[6] The study of Chatterjee et al. in India reported 739 cases with ACDR from 27,726 patients over one year, yielding a prevalence rate of 2.66%.[7] Prathap et al. in India reported 71 cases with ACDR from 14,047 patients over one year, giving a prevalence rate of 0.5%.[8] However, that research included ACDR with all types of hypersensitivity reactions. The study results are influenced by the pharmacogenetic differences on different populations, the freedom to access medicine and healthcare, drugs dosage, use of suspected drugs, and other diseases or comorbidities.[9]

The ratio of females and males was 1.1: 1. Other studies also reported the same results. Adverse drug reaction affects 1.5–1.7 times more in females than males.[10] B o rch et al. also reported the same, the ratio of females to males was 2.3:1.[6] However, Akalu and Belavadi found the opposite where adverse drug reactions due to antibiotics were observed more in males than females.[11]

Females potentially have a 1.5–1.7 times higher risk of obtaining unwanted drug reactions than males.[10] This condition can be caused by differences in pharmacokinetics, immunological factor, epigenetic, and hormonal factor between females and males. Females have more adipose tissue than males, resulting in lower hepatic clearance of drugs that areinfluenced by the enzymatic activity of cytochrome P450. As a result, it will differentiate the drug metabolism between both sexes.[12,13]

In this study, the mean age of patients with ACDR with type-IV hypersensitivity was 40.42 ± 16.30 years old. Another study showed the mean age of patients with ACDR was 52 years old.[6] Older generation poses a higher risk of suffering adverse drug reactions.[14] Unfortunately, late adulthood and elderly often have several health problems which require many treatments. The decline of visceral organ functional status greatly impacts the pharmacokinetics and pharmacodynamics of the drugs.[15]

Based on a study conducted by Alomar, elderly tend to suffer from a type-A Adverse Drug Reaction (ADR), whereas late-adulthood often receives type-B ADR. Type-A ADR is related to the action mechanism of the drugs, dysfunction of the organ, long-term effect of drug administrations, high-risk status of the patients (children, elderly, pregnancy, lactation, cancer, hemodialyzed patients).[15] Geriatric encounters immunosenescence that attenuates the capability to against antigens. Decrement of visceral organ function, long-term drug administration, and chronic diseases also influence the incidence of type-A ADR. Meanwhile, type-B ADR is related to an immune reaction and drug metabolism, so that often develops in adulthood.[16]

As shown in table 2, beta-lactam antibiotic (16.55%) was the most common drug that induced ACDR with type-IV hypersensitivity, followed by NSAID (12.18%), acetaminophen (8.62%), antiretroviral drugs (6.98%), and anticonvulsant (6.29%). Another study showed the same results that beta-lactam was the most common causative agent of ACDR.[6] Other studies also reported that antibiotics, NSAIDs, and antiepileptic drugs were the most frequent drugs that led to ACDR.[7,8] Antimicrobial agents and NSAIDs were considered common agents of ACDR.[5,17] In this study, the most frequent beta-lactams involved in ACDR were cefadroxil and amoxicillin. NSAIDs that mostly led to ACDR were mefenamic acid, diclofenac, and metamizole. Carbamazepine and phenytoin were the most common anticonvulsants involved in ACDR. These results are consistent with the study conducted by Qayoom et al.[9] Singh et al. reported 12 SJS/TEN patients out of 16 patients, i.e., more than 7.68% of total patients develop severe reactions.[18] Hence, carbamazepine and phenytoin in combination cause a more frequent and severe ACDR.

Our study showed that Maculopapular rash was the most common clinical manifestation of ACDR with a type-IV hypersensitivity induced by antibiotics. On the other side, the adverse reaction of anticonvulsant drugs and allopurinol was Stevens-Johnson Syndrome. Amoxicillin is often reported as a cause of maculopapular rashes in many patients.[19] In another study, penicillin, and quinolones are the most common causative antibiotics for an Adverse Cutaneous Drug Reaction.[20] Meanwhile, antiepileptic drugs lead to the severe manifestation of ACDR as SJS and TEN.[21]

Beta-lactam class produces a certain clinical feature because it includes hapten drugs that can directly bind to protein lysine groups and then make immunogenic reactions.[22] After binding to the protein, the drug attach to Antigen Presenting Cell (APC) because APC has Major Histocompatibility Complex (MHC) II. After that, APC activates the Cluster of Differentiation 4^+ ($CD4^+$). T lymphocytes release inflammatory cytokines, such as Interleukin- 5, Interleukin-6, Tumor Necrosis Factor (TNF) α, and interferon-γ. Cytokines regulate MHC II on endothelial cells and keratinocytes. These cells activate $CD4^+$ to produce a clinical feature as a Maculopapular rash or activate perforin and granzyme to produce a clinical feature as SJS, TEN,or FDE.[23]

Furthermore, ACDR is also affected by other factors, including the characteristics of each patient and drug. The chemical structure, dosage form, peak levels of the drugs, and immune response toward the drugs will influence adverse drug reactions. Different drug metabolism will produce different active metabolite substances that create different immune responses.[24] Different drugs also lead to the different sensitivity of patch test in diagnosing ACDR, such as beta-lactam group antibiotics, which has 39–54% sensitivity, and NSAID-related FDE has 40–87% sensitivity.[25] Hence, the detailed history taking is important to raise suspicious drug that causes ACDR.

There are many factors that affect the prognosis of ACDR, including comorbid conditions and the severity of ACDR. Research conducted by Chatterjee et al. showed that 5 of 739 ACDR patients passed away and manifested as severe ACDR likes SJS and TEN.[7]

As this is a retrospective study, researchers cannot control exposure or outcomes, so it only relies on existing data from medical records. Some samples will be missed if medical records are not complete, so it cannot cover all cases during the study period. In addition, this study only represents samples from one tertiary hospital, thus may not be representative of the larger population.

In conclusion, the prevalence of ACDR with type IV hypersensitivity is relatively low compared to the other developing countries. Maculopapular rash and Stevens-Johnson Syndrome are the most common clinical features of ACDR. Causative agents varied in each patient, dominated by antibiotics, NSAIDs, and anticonvulsants. We recommend for all healthcare providers to recognize common causative agents that often show ACDR, therefore early detection and treatment will prevent complications due to severe ACDR. Close follow-up and monitoring can be considered when healthcare providers give those agents to the patients.

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