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Original Research Article

Unveiling the clinical profiles and triggers of adverse cutaneous drug reactions at Jagakarsa general hospital

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ABSTRACT

Background: Adverse cutaneous drug reactions (ACDR) are common side effects of drug use. This study aims to analyze the characteristics of patients, clinical profiles and risk factors associated with ACDR in patients visiting the Emergency Department of RSUD Jagakarsa.
Methods: This study is a retrospective study by analyzing medical records of patients who experienced ACDR from November 2023 to October 2024. Variables analyzed included demographic data, clinical profiles, causative drugs, onset time and risk factors.
Results: There were 40 cases of ACDR with a higher prevalence in females. Patient age varied with a mean of 35.80±16.54 years. The most common clinical presentation was urticaria (42.5%), followed by angioedema (22.5%) and maculopapular rash (17.5%). The most common drugs causing ACDR were antibiotics (32.5%), NSAIDs (25%) and antihypertensives (12.5%). Most cases (70%) had an onset of less than 24 hours. Associated risk factors included a previous history of drug allergy and comorbidities such as diabetes mellitus and hypertension.
Conclusions: Increased awareness of ACDR and preventive efforts are needed to reduce the incidence and impact of ACDR.

Keywords: ACDR, Antibiotics, Retrospective

INTRODUCTION

Adverse drug reaction (ADR) according to WHO is defined as a response to a drug that is harmful and unintended, occurring at a certain dose, for prophylaxis, diagnosis and therapy of a disease.[1,2] A study in 2017-2018 found that the number of ADR patients was below 10% per year in Austria, Belgium, Greece, Latvia, Portugal and Spain, while in Lithuania, Germany and Finland, ADRs reported in patients ranged from 12% to 21%. The highest ADR reports in Europe came from Ireland and Estonia, which were at 36% in the same year.[3] In Indonesia, the prevalence of ADR ranges from 0.9% to 99% based on drug use, duration and dose of therapy.[4] Cipto Mangunkusumo Hospital (RSCM) recorded 160 cases of adverse cutaneous drug reactions (ACDR) in the period 2014-2016. Based on the total cases, 55 patients were hospitalized.[5]

Meanwhile, in another study conducted in Yogyakarta from 2011-2015, 397 out of 68,378 patients (0.58%) who visited the dermatology and venereology department of Dr. Sardjito Hospital were diagnosed with ACDR with type 4 hypersensitivity ranging from 18 months to 89

years of age.[6] The skin is one of the most common target organs for ADR (45%). ACDR or adverse drug reactions to the skin are unwanted drug effects in the form of changes in structure or function that are visible on the skin and its adnexa (nails, hair and glands).[1,2] Most ACDR manifest mildly, are self-limiting and will improve when the causative drug is stopped, but can also manifest severely or be life-threatening.

Maculopapular eruption, urticaria and fixed drug eruption (FDE) are mild manifestations of ACDR, while Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS-TEN), acute generalized exanthematous pustulosis (AGEP) and DRESS (drug reaction with eosinophilia and systemic symptoms) are severe manifestations of ACDR.[7]

Approximately 1 in 1000 hospitalized patients experience severe and life-threatening eruptions with mortality rates for DRESS, TEN, SJS-TEN and SJS of approximately 10%, 5–10%, 30% and 50%, respectively.[7]

The diagnosis of ACDR can be established based on a detailed anamnesis including complaints and history in the patient and the correlation between drug consumption and the appearance of the rash.

In the early sensitization stage, it is usually asymptomatic, then subsequent exposure can cause symptoms within seconds to minutes after exposure to the causative drug. A study reported that 279 patients (38.43%) were hospitalized within 12 hours of the onset of skin lesions. In about 28.5% of cases, the lesions appeared slowly and then spread.[9]

The pattern of ACDR and the drugs that cause it continue to change over time. All drugs can cause different types and severity of ACDR in individuals at risk for ACDR, but some drugs have a tendency to cause certain reaction patterns that provide clues to the possible drug causing the ACDR experienced by the patient.

Antibiotics (47.39%) are the most common drug category that causes ACDR followed by non-steroidal anti-inflammatory drugs (NSAIDs) 22.52%.[6,9]

According to WHO, there are risk factors for drug reactions in patients, including inappropriate drug prescription or incorrect drug dosage, patient medical history, genetics or undetected allergies, self-medication without a prescription, not following instructions for taking medication, interactions with other drugs (including traditional medicines) and certain foods.

Therefore, early detection and understanding the epidemiology of adverse drug reactions are very important in order to prevent severe manifestations.[10]

Research on ACDR in Indonesia is still limited, while the pattern of ACDR and the drugs that cause it continue to change over time. Therefore, this study aims to analyze patient characteristics, clinical presentations and risk factors associated with ACDR in patients visiting the emergency room of Jagakarsa hospital from November 2023 to October 2024.

METHODS

Study type

This is a retrospective observational study.

Study place

The study was conducted in Emergency Department of RSUD Jagakarsa.

Study duration

The study was conducted over the period from November 2023 to October 2024.

Inclusion criteria

The inclusion criteria for this study are patients diagnosed with ACDR with an identified causative drug, patients aged between 0 and 79 years with complete medical records.

Exclusion criteria

The exclusion criterion is patients with incomplete medical records.

Data collection

The data includes medical records of patients who experienced drug-induced skin allergies, with a total sample of 40 patients. The variables examined in this study include demographic factors such as gender, age, comorbidities, duration of drug reactions and history of drug allergies.

Ethical approval

Ethical approval was obtained from the Ethics Committee of RSUD Jagakarsa, with approval number KE/185/KS.01.01.

Statistical analysis

The data was analyzed using Microsoft Excel, with classification based on disease type and the number of affected patients.

RESULTS

Based on patient visit data to the Emergency Room of Jagakarsa Hospital during the period from November 2023 to October 2024, there were 40 patients who came

with ACDR conditions. Further analysis showed that women were more susceptible to ACDR than men with a prevalence of 23 women and 17 men. The average age of patients experiencing ACDR was 35.80±16.54 years with an age range between 6 years and 72 years. The age group 20-39 years dominated ACDR cases in this study. There were 6 cases where drug reactions occurred within 1-3 days after drug use.

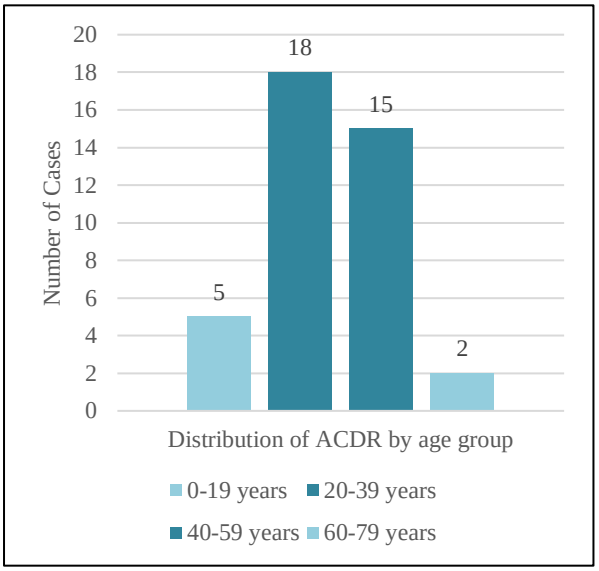

Figure 1: Distribution of ACDR by age group.

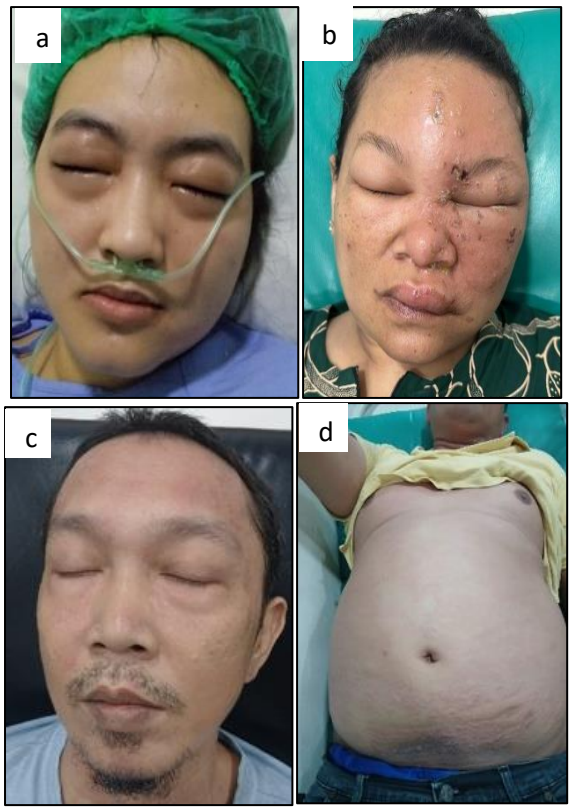

Figure 2: Angioedema (a, b) and Urticaria (c, d) induced by NSAIDs.

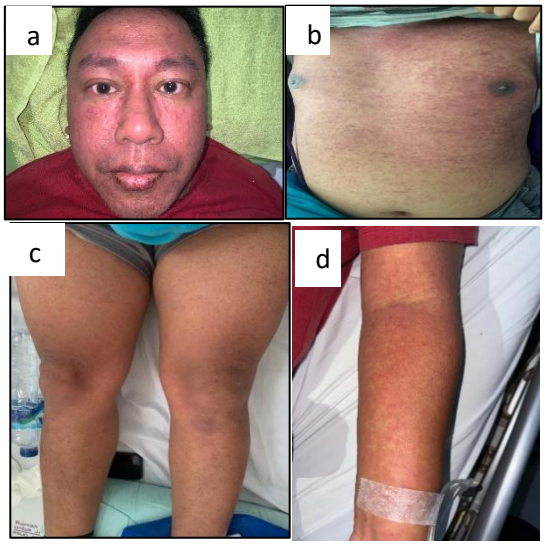

Figure 3: (a-d) Carbamazepine-induced SSJ-TEN.

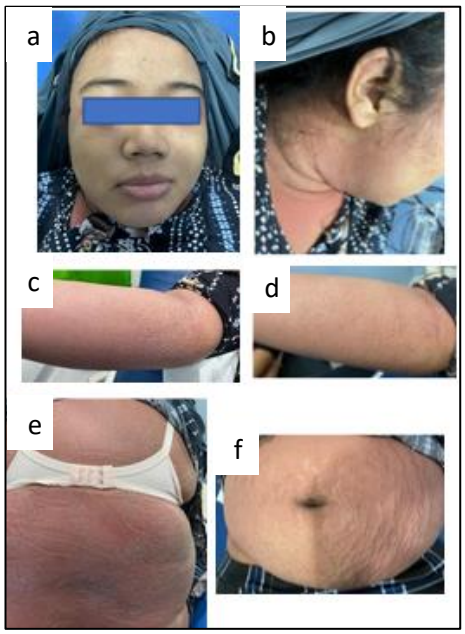

Figure 4 (a-f): Cefixime-induced AGEP.

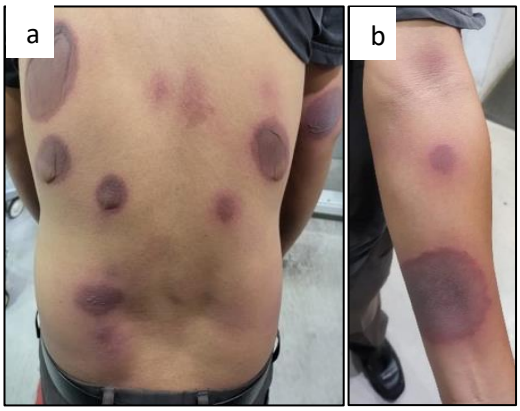

Figure 5: Allopurinol-induced FDE.

The severity of adverse drug reactions (ADRs) in this study was evaluated using the modified Hartwig and Siegel Scale. This scale divides the severity into seven categories, where categories 1-2 represent mild reactions (25 cases), categories 3-4 indicate moderate reactions (13 cases) and categories 5-7 (2 cases) indicate severe reactions. The onset time of drug reactions is generally relatively fast, which is less than 24 hours after drug use.

The study also found that 10 patients had a history of previous skin drug reactions with similar symptoms. Based on the history of the most common accompanying illnesses found in patients in this study were diabetes mellitus (4 cases) and hypertension (3 cases). Based on table 2, the drug classes that most frequently cause ACDR are antibiotics, NSAIDs and antihypertensives.

Table 1: Clinical features of ACDR.

Clinical features	No. of cases (%)	Drugs induced
Urticaria	17 (42.5%)	Antibiotics 20%, NSAIDS 7.5%, anticonvulsants 2.5%, ranitidine 5%, metformin 2.5%, antihypertensives 5%
Angioedema	9 (22.5%)	NSAIDs 15%, ranitidine 2.5%, mucolytics 2.5%, allopurinol 2.5%
Maculopapular eruption	7 (17.5%)	Antibiotics 20%, NSAIDS 2.5%, antihypertensive 7.5%, allopurinol 2.5%
SJS	1 (2.5%)	Anticonvulsants 2.5%
AGEP	3 (7.5%)	Antibiotics 5%, mucolytics 2.5%
FDE	2 (5%)	Antibiotics 2.5%, allopurinol 2.5%
DRESS	1 (2.5%)	Anticonvulsants 2.5%
Total	40 (100%)	

Table 2: Categories of drugs that induce ACDR.

Group of drugs	Total	%
Antibiotic	13	32.5
Cefixime	1	
Cefadroxil	1	
Ceftriaxone	5	
Cefotaxime	1	
Amoxicillin	2	
Rifampin	1	
Ciprofloxacin	1	
Levofloxacin	1	
NSAID	10	25
Mefenamic acid	1	
Ketorolac	1	
Diclofenac sodium	2	
Aspirin	1	
Ibuprofen	3	
Neuralgin	2	
Anticonvulsants	3	7.5
Gabapentin	2	
Carbamazepine	1	
Antihypertensi	5	12.5
Amlodipine	1	
Captopril	2	
Furosemide	1	
Ramipril	1	
Mucolytics	2	5
Guaifenesin	1	
Ambroxol	1	
Allopurinol	3	7.5
Metformin	1	2.5
Ranitidine	3	7.5

DISCUSSION

The results of the study at the Emergency Room of Jagakarsa Hospital during the period from November 2023 to October 2024, recorded that there were 40 patients who came with Adverse Cutaneous Drug Reactions (ACDR). According to Mortazavi, et al, the occurrence of ACDR generally depends on the structure and chemistry of the drug, the immune system of the individual receiving the drug, the dose of the drug, the patient's gender and the presence of certain HLA alleles.[11]

The average age of patients in our study was 35.80±16.54 years, not much different from the study by Khot, et al, who studied 70 cases and found that the average age of patients was 35.71±19.87 years.[7] The study by Ashifha, et al, found that the average age of patients was 31 to 40 years.[12] The age group that dominated ACDR cases in this study was the 20-39 years age group, similar to the study conducted by Vora RV, et al, with the most results in the 21-30 years age group with 183 cases (25.13%), followed by the 31-40 years age group with 131 cases (18.01%).[9]

Research by Khot, et al, also found that the age group most affected was 21 to 40 years old. The variation in the age range of our study patients was quite varied, ranging from 6 years to 72 years old, this result was also seen in research conducted by Khot et al, who found a variation in the age of patients from 14 years to 95 years and Vora RV, et al, found a variation in the age of patients from 2 years to 80 years.[7,9]

We found that ACDR research results were more experienced by women with a prevalence of 23 people (57.5%) while for men 17 people (42.5%). Similar to the study by Yang, et al, studied 1883 patients with significant differences in gender population, namely 65.37% female patients (n=1,231) and 34.63% male patients (n = 652).[13] Khot et al, collected ACDR patients consisting of 23 men and 47 women (the ratio of men: women is 1:2).[7]

Research by Oktarina, et al, showed a comparison of female patients with males experiencing ACDR of 1.1:1. According to the study, women potentially have a 1.5–1.7 times higher risk of experiencing adverse drug reactions compared to men. This condition can be caused by differences in pharmacokinetics, genetics, immunological factors and hormonal factors between women and men. Women have more adipose tissue than men, which results in decreased drug clearance in the liver for drugs that are affected by cytochrome P450 enzymatic activity. This causes differences in drug metabolism between the two sexes.[6]

In the study of Zucker et al, explained the disposition of drugs through several phases, namely absorption, distribution, bioavailability, metabolism and excretion which are influenced by gender differences. Smaller body weight and organ size as well as higher body fat percentage in women affect drug absorption and distribution. The magnitude of the distribution volume is directly proportional to the length of time the drug is in the body's tissues. In women, several factors such as slower gastric emptying time and lower gastric pH, lower plasma volume, lower body mass index, lower average organ blood flow and less total body water, affect the drug distribution process and pharmacokinetics.[14]

In this study, there were ACDR patients with the most comorbid histories, namely diabetes mellitus (4 cases) and hypertension (3 cases). According to Kowalska J, et al, ACDR due to antidiabetic drugs is more often experienced by the elderly group due to the pathological process experienced by the skin of diabetics related to the duration of hyperglycemia. In diabetic patients, insulin deficiency, hyperglycemia and non-enzymatic glycation (NEG) cause several complications of skin diseases such as neuropathy, microangiopathy and changes in immune response. Skin cell dysfunction occurs due to the NEG process which induces inflammation and increases oxidative stress.[15]

In this research study, there were 7 forms of ACDR that were most often found, namely urticaria, angioedema, maculopapular eruption, SJS, AGEP, FDE and DRESS. Urticaria (42.5%) was the most common form of eruption found. In accordance with the research conducted by Hidajat, et al, the most common manifestation was urticaria (32.2%), followed by FDE (25.4%), acneiform eruption (13.6%), morbilliform eruption (6.8%), maculopapular eruption (5.1%) and angioedema (3.4%).[16]

This is in accordance with a survey conducted by Khot AM, et al, the most common manifestation of ACDR was urticaria which covered 37.14%.[7] In contrast to the retrospective study conducted by Vora, et al, Maculopapular eruption was frequently seen in 182 (25%) cases followed by FDE seen in 167 (22.93%) cases and urticaria in 160 (21.97%) cases.[9]

In this study, antibiotics were the most common cause of ACDR. The beta-lactam group was the most common, with 10 cases (25%). In line with a retrospective study conducted by Makmur, et al. The most common antibiotic group found was the beta-lactam group, with 39 cases (11.11%) with the most common drug group being cephalosporins with 24 cases (6.84%).[17]

In addition to antibiotics, drugs that often cause ACDR are NSAIDs (25%). In line with the study by Makmur, et al., the three most common drug groups found were antibiotics with 76 cases (21.65%), NSAIDs with 16 cases (4.56%) and analgesics with 15 cases (4.27%).[17] According to a recent study conducted by Hidajat, et al, NSAIDs have become the most common cause of hypersensitivity reactions in the skin. NSAIDs can cause hypersensitivity reactions in the skin because NSAIDs work on arachidonic acid metabolism, thus affecting the

balance between leukotrienes and prostaglandins by inhibiting prostanoid production. The definitive mechanism of NSAID hypersensitivity is still not fully understood, but it is possible that COX inhibition caused by NSAIDs triggers excessive production of prostaglandin E2 in affected individuals.[16]

Antihypertensives are one of the most common causes of ACDR in 5 cases (7.5%) with the largest group being Angiotensin-converting enzyme inhibitor (ACEi) namely captopril. In line with the research of Castro, et al, drugs suspected in reported cases to cause skin reactions in this study were hydrochlorothiazide, furosemide, captopril and carbamazepine.

Captopril and ramipril are ACEi drugs with pharmacological mechanisms that can inhibit the breakdown of bradykinin in the lungs, where bradykinin is one of the inflammatory mediators that can trigger immunological reactions. Other studies also mention that captopril causes the same side effects, in the form of coughing and other reactions such as rash, fever and nausea.[18]

The severity of ACDR in this study was evaluated using the modified Hartwig and Siegel Scale. This scale divides the severity into seven categories, where categories 1-2 represent mild reactions (25 cases), categories 3-4 indicate moderate reactions (13 cases) and categories 5-7 (2 cases) indicate severe reactions. Similar to the results of studies conducted by Naidu, et al and Kuswaha, et al, Assessment of ADR severity using the modified Hartwig scale for 50 cases showed that the majority of ACDRs were mild, namely 27 cases (54%). Moderate ACDRs were found in 20 cases (40%), while severe ACDRs were found in 3 cases (6%).[19,20]

The time of drug reaction in this study was generally relatively fast, which was less than 24 hours after drug use. In addition, there were 6 cases where drug reactions appeared within 1-3 days after drug use. The time interval between drug use and the onset of reactions that varied on the skin depended on the type of ACDR. The same results were obtained from a study conducted by Vora, et al. The time range ranged from less than 24 hours in urticaria to three weeks to 3 months in drug reactions with DRESS. Most patients (38.43%) came within 12 hours after drug eruption.[9] In line with the study conducted by Khot AM, et al. The latency period for ACDR on average varied from less than 5 days for angioedema (16 hours) and acute urticaria (30 hours) to more than 20 days for lichenoid dermatitis and exfoliative dermatitis.[7]

This study also found that 10 patients had a history of previous skin drug reactions with similar symptoms. In a study conducted by Vora, et al, a total of 186 (25.54%) cases had a history of previous drug reactions and of these cases, around 89 (12.2%) cases had a history of reactions to the same drug previously and around 27.7% had consumed the same drug previously.[9]

This study has several limitations first, because this is a retrospective and single-center study, technical and selection bias may occur. Second, the number of samples we used was limited because not all patients reported or knew about the ACDR cases they experienced. Third, there is no universal rule to identify the exact drug that causes ACDR and this information relies on subjective examination through anamnesis and classification of ACDR skin lesions by doctors. Assessment of the time interval between drug consumption and the appearance of lesions is also a limitation of the study because patients cannot always remember this information accurately.

CONCLUSION

This study shows the importance of understanding the factors that influence the occurrence of ACDR. By increasing awareness and knowledge about ACDR, it is expected to reduce the incidence of allergic drug reactions on the skin and improve patient safety.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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