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Case Series

# Fixed Drug Eruption: A Case Series

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**Abstract**

**Background and Objectives:** Fixed Drug Eruption (FDE), is a mucocutaeous eruption occurring as a part of adverse drug reaction. They are often localised, well defined, and reoccur on the same sites upon restarting the drug. Here, we are reporting a case series of 309 patients who developed FDE after consuming these commonly used drugs.

**Methods:** This study was conducted at the dermatology outpatient department (OPD) in collaboration with the Adverse Drug Reaction (ADR) Monitoring Centre of the pharmacology department of MLB Medical College, Jhansi, under the Pharmacovigilance Programme of India. A total of 309 cases of Fixed Drug Eruption (FDE) reported between March 2014 and December 2023 were reviewed. The analysis focused on patient demographics, the type of suspected drug, and the number and distribution of FDE lesions across various body sites.

**Results:** Total of 309 patients were diagnosed with fixed drug eruption of this 274 were males and 35 were females with gender ratio of 8:1 approx. Most patient presented in the age group of 30-45 years contributing about 52.10% of patients. Antimicrobials were the most frequent culprit drugs contributing to 206 (66.67%) of 309 total cases followed by NSAIDs 100 (32.36%). In the antimicrobials fluroquinolones + Nitro-Imidazole was the commonest causing 185 (89.81%) of cases while fluroquinolone alone contributed 6 (1.94%). This was followed by penicillin + cephalosporin group 14 (4.53%) of which amoxicillin + clavulanic acid 8 (2.59%) was the commonest drug. Most common indication for drug intake was diarrhea 184(59.55%) followed by fever and pain 111 (35.92%).

**Conclusion:** Fixed drug eruptions are one of the commonest types of Cutaneous adverse drug reactions which should be assessed and reported. Since occurrence of FDE to a particular drug cannot be stopped, pigmentation often persists indefinitely and does not respond to treatment its prevention is the key. This can be done by increasing awareness and encouraging general population about the FDE, common causative drugs, and maintenance of personal drug register.

**Keywords:** Fixed Drug Eruption (FDE), Cutaneous Drug Reaction, Case Series, Skin Lesions, Erythematous Macules, Hyperpigmentation, Recurrent Lesions.



## Introduction

Fixed-drug eruption (FDE) is an immunologically mediated cutaneous adverse drug reaction marked by sharply defined hyperpigmented patches that recur at the same site upon re-exposure to the offending drug. Unlike other drug reactions, FDE does not arise spontaneously or as a result of infections; it is exclusively triggered by exogenous substances. It is the most common cutaneous drug reaction encountered in dermatology OPD [1]. The lesions often lead to persistent or even permanent hyperpigmentation. Due to its distinctive clinical presentation, FDE is typically diagnosed with relative ease compared to other cutaneous drug eruptions [2,3].

Recent studies indicate that intraepidermal CD8+ T cells are crucial in the pathogenesis of FDE. These T cells, which remain in a primed state within previously affected lesions and become activated upon re-administration of the causative drug or a chemically similar agent. Activated CD8+ T cells release interferon gamma and cytotoxic granules, including granzyme B and perforin, contributing to the inflammatory response [4]. Additionally, mast cells play a role in FDE by recruiting cell adhesion molecules on keratinocytes through tumor necrosis factor alpha, which further activates the intraepidermal T cells [5].

The aim of recent research is to delineate current trends in FDE, particularly focusing on the drugs involved and associated patient risk factors.

## Material and Method

This study was conducted at the dermatology outpatient department (OPD) in collaboration with the Adverse Drug Reaction (ADR) Monitoring Centre of the pharmacology department of MLB Medical College, Jhansi, under the Pharmacovigilance Programme of India [3,6]. A total of 309 cases of Fixed Drug Eruption (FDE) reported between March 2014 and December 2023 were reviewed. The analysis focused on patient demographics, the type of suspected drug, and the number and distribution of FDE lesions across various body sites. FDE diagnoses was based on clinical features and relevant drug histories for all patients. Detailed records, including suspected ADR reporting forms and photographs, were maintained. Patients were monitored weekly for four weeks. Causality assessment was performed using the WHO-Uppsala monitoring Centre (UMC) method and reported to the National Coordinating Centre of the Pharmacovigilance Programme of India [6,7].

## Result

Total of 309 patients were diagnosed with fixed drug eruption of this 274 were males and 35 were females with gender ratio of 8:1 approx. Most patient presented in the age group of 30-45 years contributing about 52.10% of patients. This was followed by 15-30 years age group contributing about 38.88% of the patients. (Table 1)

**Table 1**

| Age group | Male | Female | Total | Mean | Gender Ratio |
|---|---|---|---|---|---|
| 15-30 | 108 (34.95%) | 12 (3.88%) | 120 (38.83%) | 34.9903 ± 8.97 | 7.8:1 |
| 31-45 | 145 (46.93%) | 16 (5.18%) | 161 (52.10%) | | |
| 46-60 | 21 (6.80%) | 5 (1.62%) | 26 (8.41%) | | |
| 61-75 | 0 (0.00%) | 2 (0.65%) | 2 (0.65%) | | |
| Total | 274 (88.67%) | 35 (11.33%) | 309 (100.00%) | | |

Antimicrobials were the most frequent culprit drugs contributing to 206 (66.67%) of 309 total cases followed by NSAIDs 100 (32.36%). In the antimicrobials fluroquinolones + Nitro-Imidazole was the commonest causing 185 (89.81%) of cases while fluroquinolone alone contributed 6 (1.94%). This was followed by penicillin + cephalosporin group 14 (4.53%) of which amoxicillin + clavulanic acid 8 (2.59%) was the commonest drug.

NSAIDs were the second most common culprit drug category contributing to 100 (32.36%) of cases. In this group Ibuprofen + paracetamol was the commonest 49 (15.86%) followed by ibuprofen alone 14(4.53%) and paracetamol alone 14 (4.53%).

**Table 2:**

| Drug category | **Drug salt** | **Total** |
|---|---|---|
| Antimicrobials | Fluoroquinolones + Nitroimidazole | 168 (54.37%) |
| | Cephalosporin + penicillin | 14 (4.53%) |
| | Nitroimidazole alone | 11 (3.55%) |
| | Fluoroquinolones alone | 6 (1.94%) |
| | Sulfonamides | 3 (0.97%) |
| | Macrolides | 2 (0.32%) |
| | Others | 2 (0.32%) |
| Antimicrobials Total | | **206 (66.67%)** |
| Nsaids + Antipyretic | Propionic acid derivative + antipyretics | 49 (15.86%) |
| | Propionic acid derivative alone | 14 (4.53%) |
| | Antipyretics alone | 14 (4.53%) |
| | Cox 2 inhibitor alone | 14 (4.53%) |
| | Cox 2 inhibitor + antipyretics | 8 (2.59%) |
| | Salicylates | 1 (0.32%) |
| Nsaids + Antipyretic Total | | **100 (32.36%)** |
| Antifungal | Azole | 3 (0.97%) |
| Total | | **309 (100.00%)** |

Most commonly patients presented within 24 hours of drug intake 107 (34.63%) followed by 24-48 hours 91(29.45%), while in duration of 48-72 hours 52 (16.83%) of patient experience FDE. Within 48

hours antimicrobials were common culprit drug while after 96 hours NSAIDs were approximately 4 times more common. (Table 3)

**Table 3:**

| Drug Cat | 0-24h | 24-48h | 48-72h | 72-96h | >96h | Total |
|---|---|---|---|---|---|---|
| Antimicrobials | 79 (25.57%) | 64 (20.71%) | 34 (11.00%) | 19 (6.15%) | 10 (3.24%) | **206 (66.67%)** |
| Nsaids + Anti-pyretic | 27 (8.74%) | 25 (8.09%) | 18 (5.83%) | 15 (4.85%) | 15 (4.85%) | **100 (32.36%)** |
| Antifungal | 1 (0.32%) | 2 (0.65%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | **3 (0.97%)** |
| Total | **107 (34.63%)** | **91 (29.45%)** | **52 (16.83%)** | **34 (11.00%)** | **25 (8.09%)** | **309 (100.00%)** |

Most common indication for drug intake was diarrhea 184(59.55%) followed by fever and pain 111 (35.92%). (Table 4)

**Table 4:**

| Indication | Anti microbials | NSAIDs + Antipyretic | Antifungal | Total |
|---|---|---|---|---|
| Diarrhoea | 184 (59.55%) | 0 (0.00%) | 0 (0.00%) | 184 (59.55%) |
| Fever + Pain | 11 (3.56%) | 100 (32.36%) | 0 (0.00%) | 111 (35.92%) |
| Others | 11 (3.56%) | 0 (0.00%) | 3 (0.97%) | 14 (4.53%) |
| Total | 206 (66.67%) | 100 (32.36%) | 3 (0.97%) | 309 (100.00%) |

In most of the cases drugs were prescribed by local practitioner 109 (35.82%) whose degree was not known to patients followed by self-administration 86 (27.83%) and dispensed by medical store person 67 (21.68%) directly. (Table 5)

**Table 5:**

| Medicine Prescribed By | Total |
|---|---|
| Local Doctor degree not specified | 109 (35.28%) |
| Self Admin or advised by others (family, friends) | 86 (27.83%) |
| Medical Store | 67 (21.68%) |
| Registered medical practitioner | 47 (15.21%) |
| Grand Total | **309 (100.00%)** |

Most commonly extremities were involved 95 (30.74%) followed by face & oral mucosa 83 (26.86%), trunk in 67 (21.68%) and genital mucosa 64 (20.71%). (Table 6)

**Table 6:**

| Site of FDE | Total |
|---|---|
| Extremities | 95 (30.74%) |
| Face & Oral Mucosa | 83 (26.86%) |
| Trunk | 67 (21.68%) |
| Genital | 64 (20.71%) |
| Total | 309 (100.00%) |

In most of the patients single lesion was seen 127 (41.10%) followed by presence of 2-5 lesions 117 (37.86%). Only in 65(21.04%) cases more than 6 lesions were present.(Table 7)

**Table 7:**

| No. of Lesions | Total |
|---|---|
| 1 | 127 (41.10%) |
| 2 to 5 | 117 (37.86%) |
| 6 or More | 65 (21.04%) |
| Total | **309 (100.00%)** |

All causative drugs were orally administered, and Causality assessment was done by using the WHO-Uppsala causality assessment which was possible in all cases.[7]

The FDEs were treated by discontinuing the offending drug and if required than with topical corticosteroids, and oral antihistamines. Patients not responding to conservative treatment were treated with tapering dose of oral steroids. Majority of the Patients recovered in 7 days, while in few patients, the lesions took 2 weeks to resolve. In all these patients, there was persistent hyperpigmentation of the affected site till last follow-up. [8]

## Discussion

Our study represents one of the largest case series of Fixed Drug Eruption (FDE) reported to date, comprising a total of 309 patients. This series demonstrated a predominance of males (274 males and 35 females). The higher incidence in males may be attributed to increased reporting rates among males or a potential underreporting by females, possibly due to milder nature of reactions or lower drug intake among women. Historically, some case series have shown a female predominance. FDE has been reported to account for 14%–22% of cutaneous drug reactions in children; however, none were observed in our study [3,6].

Consistent with findings from other studies, antimicrobials and non-steroidal anti-inflammatory drugs (NSAIDs) were the most common classes of drugs causing FDE in our series [13]. Among antimicrobials, fluoroquinolones and nitroimidazoles were the most frequently implicated, aligning with several other case series [3,6,8,14,15]. Although sulfamethoxazole-trimethoprim and doxycycline were previously more commonly associated with FDE, their decreasing use has led to a reduction in FDE cases linked to these drugs. Similar to our study, most cases involved drugs prescribed for diarrhea, fever, and pain [3,11]. Variations in causative drugs across different regions may be influenced by factors such as self-medication practices, genetic predispositions, concurrent use of multiple drugs, and regional drug preferences.

In our study, the most frequently affected sites were the extremities (30.74%), followed by the face and oral mucosa (26.86%). These sites are commonly recognized as areas of involvement in FDE according to several studies [3,11]. Many cases of generalized FDE initially presented as localized lesions that get generalized with recurrent drug exposure [3,8,13,14,15].

As in most studies, the oral route was the most common method of drug administration in our series. Patients with unidentified culprit drugs were excluded from the study. Previous research by Lee et al. found that offending drugs were not identified in 71.6% and 23% of cases, respectively [10]. Difficulties in determining the causative drug often arise from concurrent medication use, inaccurate patient histories, and non-drug-related causes of FDE [9]. FDE cases were more frequent among patients receiving prescriptions from local doctors whose degree was not known as they are in direct contact with peripheral patients in rural and small-town settings.

Adverse reactions are rarely specific to a single drug, and diagnostic tests are often unavailable. Rechallenge is rarely ethically justified. Consequently, most adverse reactions are classified as 'possible' or 'probable,' with few reaching the extremes of 'certain' or 'unlikely.' To address these challenges, various structured systems for causality assessment have been developed [7,12]. According to the WHO-Uppsala Monitoring Centre causality assessment system, the adverse reactions in our study were classified as 'possible' reactions to fluoroquinolones and other drugs [12].

## Conclusion

Fixed drug eruptions are one of the commonest types of Cutaneous adverse drug reactions which should be assessed and reported. Since occurrence of FDE to a particular drug cannot be stopped, pigmentation often persists indefinitely and does not respond to treatment its prevention is the key. This can be done by increasing awareness and encouraging general population about the FDE, common causative drugs, and maintenance of personal drug register.

With the decrease use of sulphonamides nowadays fluroquinolones have now become the commonest culprit drugs followed by NSAIDs. Accordingly, most common indication for drug intake was diahorrea followed by fever and pain. Another highlight of the study was drug intake after being prescribed by local practitioner whose degree and pathy was not known to patients. This was followed by self-administration and dispensed by medical store directly. More research is required to know why it usually occurs usually after oral intake of drugs and its less prevalence in children.

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