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DRUG-INDUCED URTICARIA: IMPLICATED DRUGS, REACTION RECOVERY TIME AND CAUSALITY ASSESSMENT -A FIVE-YEAR RETROSPECTIVE STUDY

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Keywords:

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ABSTRACT: Introduction: Cutaneous Adverse drug reactions presenting as urticaria are the most frequent local and systemic adverse reactions (ADR). Urticaria is a skin disorder resulting from the vascular reaction of the skin characterized by erythema and wheal formation due to a localized increase of vascular permeability. It affects up to 20 % of the population at some point during their life and can be acute or chronic. Acute Urticaria can be etiologically due to infection, drugs, and food; and usually resolves within ≤ 6 weeks. Itching and rash are diagnosed clinically due to either type I hypersensitivity (IgE dependent) or type III hypersensitivity Immune complex. **Material and Methodology:** This 5-year retrospective observational study was conducted at Pt. JNM Medical College associated with DR. BRAM Hospital. All Individual Case Safety Reports (ICSRs) were analyzed from the Adverse Drug Reaction Monitoring Centre (AMC) database under PvPI between 1st January 2018 to 31st December 2022, and all Drug induced Urticaria were included. **Results:** Of the total 1425 ICSRs, 53(3.7%) reactions were identified as Urticaria with female preponderance (58.4%), and parenteral routes accounted for 58.4% of cases. Antibiotics were the most common offenders (45.2%) where Beta-lactams accounted for 32% of reactions, and prominently feature ceftriaxone a third-generation Cephalosporin responsible for 15% of total urticaria. This was followed by analgesic paracetamol (13.2%), and anti-rabies vaccine 5.6%. The reaction subsided within 1 day in 39.6% of cases, 2 days in 49 %, and 3- 7 days in 11.3% of cases. According to the WHO -UMC Causality scale 84.9 % were "probable" and 2 cases were "certain" and where due to Vancomycin and FDC of ibuprofen paracetamol. **Conclusion:** Beta-lactam antibiotics (ceftriaxone) are the most common cause of drug-induced urticaria, early onset and resolution suggest they are acute urticaria and the majority were probable.

INTRODUCTION: Cutaneous adverse drug reactions are seen in 2-3 % of hospitalized patients and are the most frequent local and systemic adverse reactions to commonly used drugs. These present as urticaria, maculopapular eruptions/rash, or fixed drug reactions presenting as erythematous or hyperpigmented lesions.

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These reactions may occur be acute and occur immediately or chronic and appear up to 4 weeks after initiation of therapy and are usually unpredictable. They are mild to severe and may be self-limiting or require long-term treatment [1].

Urticaria is a common skin condition affecting up to 20% of the population during their lifetime, with a current prevalence of 1% [2]. Urticaria also called hives or welts is an allergic/ hypersensitivity reaction that may present as swelling of varying sizes, surrounded by reflex erythema. It may cause symptoms such as transient itching or burning resembling insect bites or nettle stings [3].

Urticaria may or may not be accompanied by angioedema which is characterized by sudden and pronounced swelling of the lower dermis and subcutis, and may take up to 72 hours to resolve. Urticaria can appear on any part of the body with the trunk being the most commonly affected followed by the palms, soles, and scalp. Prompt recognition of severe reactions, drug withdrawal, and therapeutic intervention can minimize the severity [4]. Urticaria can be due to a) allergic reaction to food or insect bite b) heat or cold exposure c) infections d) medication like NSAIDs, or beta-lactam antibiotics e) contact urticaria due to nickel or lead f) and idiopathic. Drug-induced urticaria is diagnosed by a positive history of drug intake and presents clinically as the sudden emergence of red, itchy skin welts resembling insect bites and can cause a burning sensation and appear on palms, soles, and scalp, with the trunk being the most commonly affected area. The urticarial rash can occur alone or with other symptoms like angioedema, systemic symptoms, or anaphylaxis. Systemic symptoms such as hypotension, dyspnea, and anaphylaxis may be seen [5].

In acute drug-induced urticaria, skin rash appear within a few hours to a few days after taking the drug, but typically disappears within 72 hours of withdrawing the suspected drug. In chronic drug-induced urticaria, the condition can recur over a prolonged period, with the urticaria resolving and returning intermittently for more than 6 weeks. The immune system recognizes a medication as foreign and mounts an allergic response releasing histamine and other chemicals resulting in a rash and itching, while in some cases non allergic mechanisms, either immunological or non-immunological processes are responsible for urticaria [6]. Drug-induced urticarial reactions can be IgE-mediated allergic reactions (type I) also known as anaphylaxis as seen with B lactam antibiotics, some vaccines, and polypeptide hormones [7].

Urticaria due to circulating immune complex-mediated Type III hypersensitivity reaction occurs one to two weeks after exposure and resolves within several weeks of discontinuation of medications seen with drugs containing heterologous antigens like vaccines (rabies, rubella, inactivated influenza, pneumococcal, and hepatitis B vaccines), immune-modulating agents (rituximab, infliximab), and anti-venoms [8]. Non-immunologic urticaria is seen with certain medications that directly stimulate histamine release from mast cells, independent of an allergic response as seen due to antisera, amoxicillin, aspirin, and NSAIDs [9]. Histamine-induced vasodilation, increased vascular permeability, and smooth muscle contraction lead to the characteristic red, raised, and itchy hives seen in urticaria. Complement activation and release of anaphylatoxins lead to the development of anaphylactic reactions [10]. Drugs implicated in urticaria include antibiotics (like penicillin and sulfa drugs), non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen, certain blood pressure medications, ACE inhibitors, opioids, some vaccines and antivenoms, and contrast agents [11]. Moat cases of urticaria are self-limiting and resolved by withdrawing the triggering drug. Antihistaminic and corticosteroids help in relieving the symptoms [6]. Very few studies have been conducted in this region to identify the drug-causing urticaria, reaction recovery time, and causality assessment, so this study was undertaken.

MATERIAL AND METHODOLOGY: This 5-year retrospective study "Drug-Induced Urticaria: Implicated Drugs, Reaction Recovery Time and Causality Assessment -A Five-Year Retrospective Study" was conducted at Pt. JNM Medical College is associated with DR. BRAM Hospital. All ADR reports termed individual case safety reports (ICSRs), were analyzed from the database of AMC under PvPI between 1st January 2018 to 31st December 2022, and all reactions of urticaria were included. Ethical approval was taken from the institutional ethical committee, (Mc/ethics/2023/85/Dt28/11/2023).

RESULTS: A total of 1425 ADRs were reported during this period and 53 (3.7%) ADRs of Urticaria were identified with 53 cases, female preponderance (58.4%) was observed **Fig. 1**, parenteral route accounted for 58.4% of reactions **Fig. 2**. Among the drugs causing Urticaria, antibiotics were implicated in 45.2% of cases **Fig. 3.** Among the individual classes of drugs, beta-lactams accounted for 32.0 % of which ceftriaxone alone was implicated in 15% of cases. This was followed by analgesic paracetamol (13.2%), and

anti-rabies vaccine (5.6%) **Table 1.** The reaction subsided within 1 day in 39.6% of cases, 2 days in 49 %, and 11.3% took 3- 7 days to subside **Fig. 4.** According to the WHO -UMC Causality scale 84.9 % were 'probable', 11.4 % were possible and 3.7% of cases were 'certain' and were due to Vancomycin and the fixed-dose combination of Ibuprofen-paracetamol **Fig. 5.**

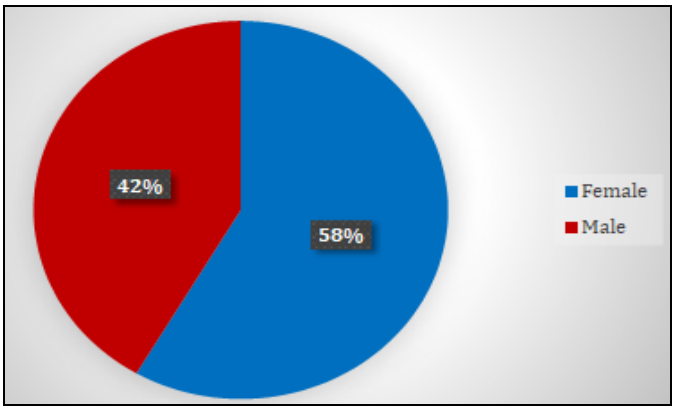

FIG. 1: URTICARIAIN MALEAND FEMALE

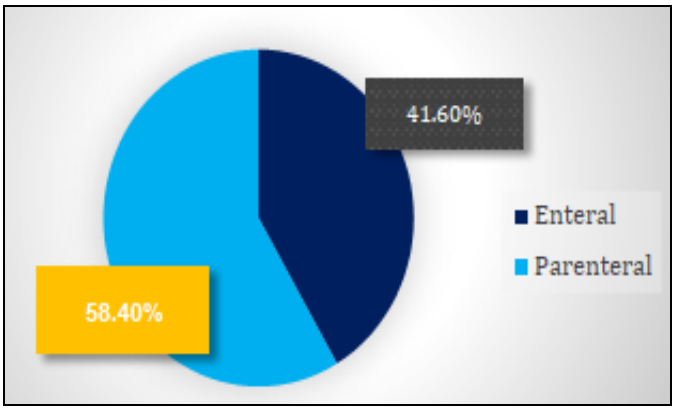

FIG. 2: ROUTES OF DRUG ADMINISTRATION

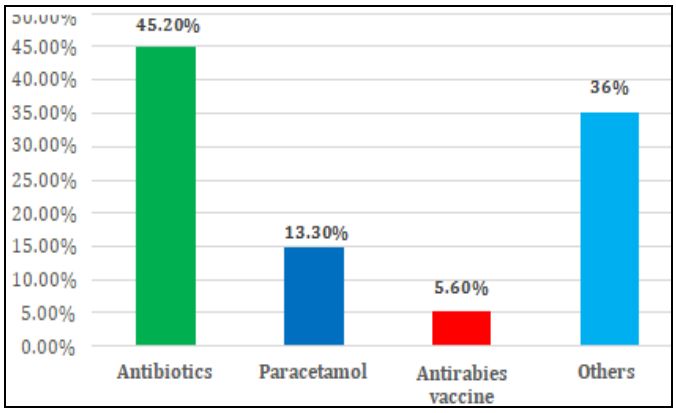

FIG. 3: DRUGS CAUSING URTICARIA

TABLE 1: DRUG CAUSING URTICARIA

S. no.		Drug	Number n=53	Percentage (%)
1.	**Antibiotic**	Ceftriaxone	8	15.09%
2.		Ciprofloxacin	3	5.6%
3.		Amoxicillin and Calvinic acid	3	5.6%
4.		Norfloxacin and tinidazole	2	3.77%
5.		Amoxicillin	2	3.77%
6.		Vancomycin	2	3.77%
7.		Cotrimoxazole	1	1.88%
8.		Piperacillin	1	1.88%
9.		Piperacillin and tazobactam	1	1.88%
10.		Ampicillin	1	1.88%
1	**NSAIDs**	Paracetamol	7	13.6%
2.		Diclofenac	2	3.77%
3.		Paracetamol and Acelofenac	1	1.88%
4.		Ibuprofen+Paracetamol	1	1.88%
1.	**Others**	Antirabiesvaccine	3	5.6%
2.		Pantoprazole	2	3.77%
3.		Metronidazole	2	3.77%
4.		Ondansetron	1	1.88%
5.		Dicyclomine+Mefenamic acid	1	1.88%
6.		Omeprazole	1	1.88%
7.		Fluconazole	1	1.88%
8.		Methyl prednisolone + folic acid+Mesalazine	1	1.88%
9.		Omipaque	1	1.88%

10.	Cytarabine	1	1.88%
11.	L-Aspringine	1	1.88%
12.	Rituximab	1	1.88%
13.	Ferrous Ascorbate+Folic Acid	1	1.88%
14.	Dextrose Saline	1	1.88%

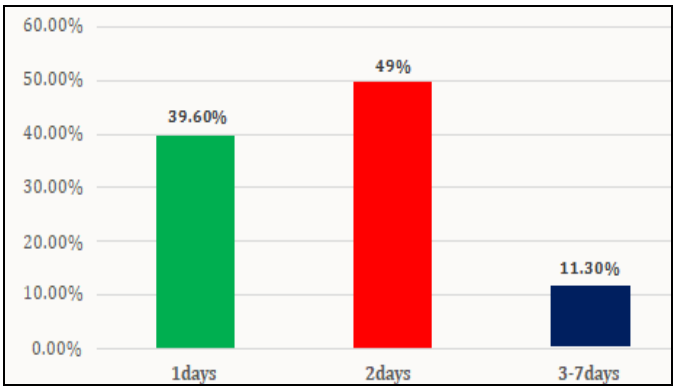

FIG. 4: REACTION RECOVERY TIMING

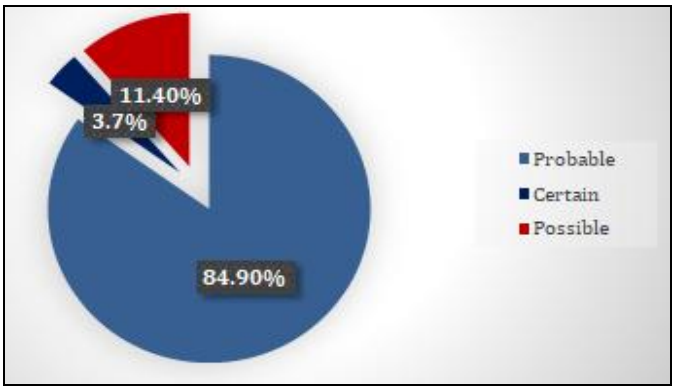

FIG. 5: WHO-UMC CAUSALITY SCALE

DISCUSSION: Urticaria is a common presentation of cutaneous adverse drug reactions. In this study drug-induced urticaria accounted for 3.7% of all ADRs with female preponderance (58.4%). This finding aligns with other studies that reported a greater susceptibility among women [12-14]. This heightened incidence in females can be attributed to the influence of sex hormones on regulating inflammation and immune responses. Estrogen, enhances the activity of T-helper cells, thereby amplifying the immune response and potentially increasing the risk of urticarial reactions [15].

Additionally, hormonal fluctuations during menstrual cycles, pregnancy, and menopause might contribute to this heightened susceptibility [16]. These factors underscore the importance of considering sex-specific responses in the diagnosis of drug-induced urticaria. The parenteral route accounted for 58.4% of urticarial reactions. Parenteral administration leads to direct entry of the drug into the bloodstream, bypassing the gastrointestinal tract, facilitating quicker antigen presentation, and provoking immediate antibody formation, emphasizing the need for careful monitoring and pre-administration sensitivity screening to mitigate urticarial adverse effects [17].

Among the drugs causing urticaria, Antibiotics were the most common offenders (45.2%). Beta lactams accounted for 32% of reactions, and prominently feature ceftriaxone a third-generation Cephalosporin that was responsible for 15% of total urticaria cases and is consistent with a study by Uliano S *et al* who also reported 31.9% cases of urticaria due to Beta Lactams [18]. However, Patel *et al* reported clotrimazole (18.5%) as the most common drug causing urticaria and Jha *et al.* noticed that the most common drug causing urticaria was cephalosporin (27.27%), followed by NSAIDs (23.64%) and fluoroquinolones (14.54%) [19, 20]. The substantial impact on urticaria incidence due to ceftriaxone in this study is its widespread use and availability in hospital supply for treating all infections, and its propensity to elicit immune responses [21].

Paracetamol which is implicated in 13.2% of urticarial reactions is notable given its extensive use as an analgesic and antipyretic, although generally considered safe, its metabolites act as haptens, inducing an immune response leading to urticaria [22]. This is in contrast to a study by Kasemsarn *et al* who reported that among NSAIDs, ibuprofen accounted for 25.7% of the urticarial rash followed by celecoxib [23].

The mechanism by which NSAIDs like Ibuprofen, paracetamol, and diclofenac (those derived from the pyrazole group) produce hypersensitivity reaction and urticaria is by inhibiting COX -1 which increases the production of leukotrienes which recruits immune cells which is recognized as a constituent of the allergic mediator slow reacting substance of anaphylaxis [24]. The anti-rabies vaccine, which accounted for 5.6% of urticarial reactions, highlights the immunogenic potential of vaccines, although crucial for its

protective effect, can occasionally lead to hypersensitivity and urticaria [25]. The rabies post exposure prophylaxis regimen guide for health professionals' states that urticaria occurs in 6% of pre-exposure-vaccinated individuals receiving a booster dose of rabies vaccine after primary vaccination [26]. This observation stresses the need for active surveillance of cutaneous adverse events especially urticaria following immunization (AEFI) in patients receiving all vaccines, including pre- and post-exposure prophylaxis. Time to resolution is one day in 39.6 % of cases, 2 days in 49.0 % of cases, and 3-7 days in 11.3 % of cases following the discontinuation of the causative drug. This rapid recovery indicates that the cessation of the offending drug typically leads to a swift resolution of symptoms as the drug and its metabolites are cleared from the body [27].

However, rabies vaccine-induced urticaria presented as an exception as it persisted longer. The prolonged presence of vaccine antigens in the body may contribute to a more sustained immune reaction, extending the duration of urticaria, and the need to monitor patients for an extended period following vaccination. According to 'The WHO Causality Scale'11% of ADRs were "possible" indicating a less certain link between drug exposure and urticaria. The "probable" ADRs in the majority (85%) of cases indicate a strong temporal relationship between drug administration and the onset of urticaria, typically supported by improvement upon drug withdrawal but lacking definitive re-challenge evidence [28]. Urticaria due to Ibuprofen with Paracetamol (PCM) and Vancomycin was "certain" as the rechallenge was positive and emphasizes the need for eliciting a history of drug reaction so these ADRs can be prevented. Vancomycin is well known to cause red man syndrome in 3.7 % - 47% when given by both oral and parenteral route which is due to direct degranulation of mast cells and basophils and in non-immunological. Though it is self-limiting and may require treatment with antihistamines in mild and moderate cases but requires stoppage of the drug in cases where urticaria is associated with a severe reaction [29].

Major limitations of this study include its being based on retrospective data and data from only one hospital. A large population of patients suffer from drug-induced urticaria and those reporting to the hospital are the tip of the iceberg given the availability of prescription drugs (including antimicrobials) without prescription in India. Ignorance about allergy to drugs and urticaria as one of the symptoms and fear of reporting also leads to underreporting.

CONCLUSION: All clinicians and patients along with their relatives should be sensitized to recognize urticaria as an ADR especially when prescribing well-known offending drugs like Beta-lactam antibiotics, especially third-generation cephalosporins, and NSAIDs. This will allow early diagnosis and therapeutic decision-making for patient safety and management. There is a need for larger cohort studies considering the prescription pattern in India to find the accurate incidence and drug-induced urticaria.

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