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A MANUAL ON DRUG ALLERGY - A COMPREHENSIVE REVIEW

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INTRODUCTION

All drugs have the potential to cause side effects, also known as 'adverse drug reactions', but not all of these are allergic in nature .A drug allergy, or an allergic drug reaction, is a type B adverse drug reaction that results from a specific immunologic response to a medication. Allergic drug reactions account for about 6 to 10 percent of all adverse drug reactions, but up to 10 percent of fatal reactions. IgE, IgG, can mediate immunologic drug reactions or by lymphocytes. Drug-specific immune responses depend on host factors and on the chemical structure and metabolism of the drug.

A pseudo allergic drug reaction is a reaction that is similar or identical in presentation to an immunologic reaction, but is NOT mediated by the immune system.

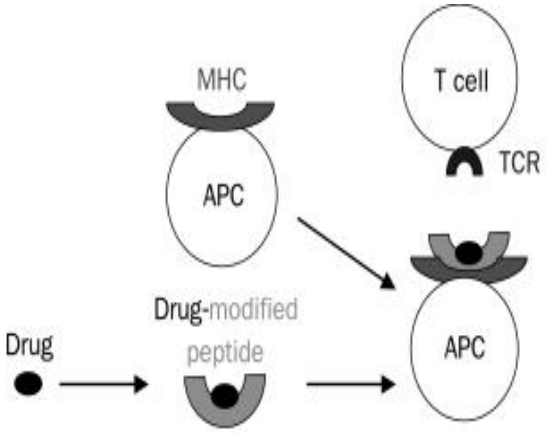
Statitics

- Worldwide, adverse drug reactions may affect up to 10% of the world's population and affect up to 20% of all hospitalized patients.
- Worldwide, drugs may be responsible for up to 20% of fatalities due to anaphylaxis.
- Hospital Episode Statistics from 1996 to 2000 reported that drug allergies and adverse drug reactions accounted for approximately 62,000 hospital admissions in England each year. There is also evidence that these reactions are increasing: between 1998 and 2005, serious adverse drug reactions rose 2.6-fold. Up to 15% of inpatients have their hospital stay prolonged as a result of an adverse drug reaction.
- About half a million people admitted to NHS hospitals each year have a diagnostic 'label' of drug allergy, with the most common being penicillin allergy. About 10% of the general population claim to have a penicillin allergy.
- Allergic reactions to non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, diclofenac, naproxen and aspirin, are common. In particular, 5–10% of people with asthma are affected.
- Anaphylaxis-type reactions occur in approximately 1 in 1000 of the general population. Anaphylaxis during general anesthesia occurs in 1 in 10,000–20,000 anesthetics.
- Analysis of patient safety incidents reported to the National Reporting and Learning System (ENGLAND) between 2005 and 2013 identified 18,079 incidents involving drug allergy. These included 6 deaths, 19 'severe harms', 4980 'other harms' and 13,071 'near-misses'. The majority of these incidents involved a drug that was prescribed, dispensed or administered to a patient with a previously known allergy to that drug or drug class.

Mechanism of Drug Allergy

A drug allergy, or an allergic drug reaction, is a type B adverse drug reaction. Type B are hypersensitivity reactions, mediated by immunologic or other types of mechanisms, which occur in a susceptible subgroup of patients, have signs and symptoms that are different from the pharmacologic actions of the drug, and usually cannot be predicted.

Drugs are too small to elicit an immune response. Thus, to be immunogenic, they are thought to act as haptens or prohaptens. Haptens are chemically reactive small molecules (mostly <1000 D) that bind covalently to a larger protein or peptide. Prohaptens are inert drugs that undergo metabolism (bio activation) and become reactive metabolites (haptens), which then can bind covalently to proteins. T-cell sensitization occurs when such drug-protein complexes (hapten-carrier complexes) are taken up by antigen-presenting cells (APCs) and then transported into the local draining lymphoid tissue, where they are processed and presented on major histocompatibility complexes (MHCs). There, naïve T cells with the appropriate specificity recognize these complexes, are induced to proliferate, and expand as primed T cells.



Specific T-cell recognition of drug-carrier compounds (hapten/prohapten concept). Drug/drug-metabolite carrier compounds are presented on antigen-presenting cells (APCs), where T cells with appropriate T-cell receptors (TCRs) recognize them. MHC = major histocompatibility complex

Hapten-carrier complexes may be antigenic for both T cells and B cells. In the presence of specific T-cell help, drug-specific B cells may proliferate and differentiate into plasma cells.
After primary sensitization to a causative drug, a second exposure causes affected T cells and antibodies to enter the elicitation phase, corresponding to the type I to IV immune reactions

Systematic Approach to The Patient- If Allergic Reaction Suspected
The patient in intensive care who develops a rash while receiving multiple medications, or the ambulatory patient with complex chronic diseases who develops a new and unexplained symptom while taking many medications.

The main questions that arise in such situations include the following:

- Is the adverse event related to a drug.
- If so, which drug is responsible?
- Is the reaction due to an immune response to the drug (i.e., true drug allergy) or due to another mechanism, such as pseudo allergy?
- If the reaction is a drug allergy, what is the likely mechanism?
- How can necessary therapy for the underlying medical problem be continued.

Drug desensitization
If there is no suitable alternative to the drug allergic to, need to undergo drug desensitization. This involves taking the drug in increasing amounts until the person can tolerate the needed dose with minimal side effects. This will most likely be done in a hospital so immediate medical care is available if problems develop.

Desensitization can help only if the drug istaking every day. , when a chemotherapy cycle ends – we need to go through desensitization a second time if need the drug again.

Management of anaphylaxis
The most common signs and symptoms of anaphylaxis are cutaneous (eg, sudden onset of generalized urticaria, angioedema, flushing, and pruritus). However, 10 to 20% of patients have no skin findings. Danger signs: Rapid progression of symptoms, respiratory distress (eg, stridor, wheezing, dyspnea, increased work of breathing, persistent cough, cyanosis), vomiting, abdominal pain, hypotension, dysrhythmia, chest pain, collapse.

Acute management: The first and most important treatment in anaphylaxis is epinephrine. There are NO absolute contraindications to epinephrine in the setting of anaphylaxis.

Airway: Immediate intubation if evidence of impending airway obstruction from angioedema. Delay may lead to complete obstruction. Intubation can be difficult and should be performed by the most experienced clinician available. Cricothyrotomy may be necessary.

Promptly and simultaneously, give:

IM epinephrine (1 mg/mL preparation): Give epinephrine 0.3 to 0.5 mg intramuscularly q5 - 15minutes prn, preferably in the mid-outer thigh. Most patients respond to one, two, or at most, three doses. If symptoms are not responding to epinephrine injections, prepare IV epinephrine for infusion, at a rate 0.1 mcg/kg/minute by infusion pump. Titrate the dose continuously according to blood pressure, cardiac rate and function, and oxygenation.

Place patient in recumbent position, if tolerated, and elevate lower extremities. Oxygen: Give 8 to 10 L/minute via facemask or up to 100% oxygen, as needed. Normal saline rapid bolus: Treat hypotension with rapid infusion of 1 to 2 liters IV. Repeat, as needed. Massive fluid shifts with severe loss of intravascular volume can occur.

Albuterol (salbutamol): For bronchospasm resistant to IM epinephrine, give 2.5 to 5 mg in 3 mL saline via nebulizer. Repeat, as needed.

Adjunctive therapies:
H1 antihistamine: Consider giving diphenhydramine 25 to 50 mg IV (for relief of urticaria and itching only).
H2 antihistamine: Consider giving ranitidine 50 mg IV.
Glucocorticoid: Consider giving methylprednisolone 125 mg IV.

Monitoring: Continuous noninvasive hemodynamic monitoring and pulse oximetry monitoring should be performed. Urine output should be monitored in patients receiving IV fluid resuscitation for severe hypotension or shock.

Treatment of refractory symptoms: Vasopressors: Some patients may require a second vasopressor (in addition to epinephrine).

Glucagon: Patients on beta-blockers may not respond to epinephrine and can be given glucagon 1 to 5 mg IV over 5 minutes, followed by infusion of 5 to 15mcg/minute. Rapid administration of glucagon can cause vomiting.

1. Penicillin Allergy

Among the drugs associated with IgE-mediated allergic reactions, penicillin's are most commonly implicated. Penicillin allergy is estimated to affect 7% to 10% of community populations and up to 20% of hospitalized patients. However, when penicillin allergy testing is performed in individuals who report a history of penicillin allergy, the overwhelming majority do not exhibit positive reactions. The American Academy of Allergy, Asthma and Immunology states that approximately 10 percent of people report having a penicillin allergy
-- but greater than 90 percent might not be truly allergic.

A frequent clinical question is whether these patients can safely receive the structurally related cephalosporins or carbapenems. There is morbidity, mortality, and economic cost associated with the unnecessary withholding of penicillin's in patients who are labelled as allergic based on history alone. Patients with a history of penicillin allergy are more likely to be treated with broad-spectrum antibiotics, such as quinolones or vancomycin .There are distinct disadvantages to broad-spectrum agents, which are often more expensive, associated with more side effects (such as Clostridium difficile infection), and less effective for some infections . In addition, overuse of vancomycin and quinolones contributes to the development and spread of certain types of drug-resistant bacteria.

There should be an evidence-based, pragmatic approach based on categorization of the past reaction and for those patients with possible immediate (eg, immunoglobulin E [IgE]- mediated) allergy, an assessment of the risk of a recurrent immediate reaction. this permits a large majority of patients labelled as penicillin-allergic to receive related beta-lactam antibiotics with minimal risk of acute allergic reactions.

Acute (Type I) IgE mediated reaction

- Anaphylaxis, hypotension, vasodilation, bronchospasm, angioedema, and urticaria, bowel edema, cardiovascular collapse, death
- Detected by skin test
- Uncommon (less than 2% of penicillin allergies)
- Occurs immediately (within minutes to hours); mostly after parenteral administration
- Do not give another type of penicillin (eg cephalosporin) in this population
- IgE decreases 10% per year to around 30% after 10 years
- Nonacute (Type I, II, IV) T-cell mediated reaction
- Fever, arthralgia, arthritis, urticaria, anemia, thrombocytopenia, serum sickness, vasculitis.
- Not reliably detected by skin test; can be detected by in-vitro testing
- May occur 24 to 36 hours following administration in patients previously exposed and 7 to 10 days in those not previously sensitized

Alternatives

1. **Macrolides** -are effective against a similar range of bacteria as penicillin, which makes them a good alternative. They are structurally different from the penicillin's and, therefore, are generally considered safe for people with a penicillin allergy. Examples: erythromycin, clarithromycin, azithromycin.
2. **Newer Cephalosporins**-Roughly 10 percent of people with a penicillin allergy also react to cephalosporins. This phenomenon, known as cross-reactivity, is most likely with older cephalosporins. Third generation and other newer cephalosporins are generally considered relatively low risk in terms of penicillin allergy cross-reactivity.Eg: cefdinir, cefixime.
3. A number of other antibiotics might be considered to treat an infection in someone who is allergic to penicillin. These include but are not limited to: Fluoroquinolones (ciprofloxacin) – clindamycin, doxycycline, tetracycline, trimethoprim-sulfamethoxazole (Bactrim), aztreonam (Azactam), vancomycin.

Alternative in Specific conditions

Urinary Tract Infections	
Female Lower UTI	Trimethoprim or nitrofurantoin
Female Upper UTI	Co-trimoxazole + gentamicin
Male UTI	Trimethoprim or ciprofloxacin
Upper Respiratory Tract Infections	
Sinusitis	Doxycycline
Tonsillitis	Erythromycin or clarithromycin
Otitis Media	Erythromycin or clarithromycin
Lower Respiratory Tract Infections	
Community Acquired Pneumonia (non-severe)	Doxycycline
Community Acquired Pneumonia (severe)	IV Levofloxacin then oral doxycycline

Aspiration or Hospital Acquired Pneumonia (severe)	IV Vancomycin + metronidazole +gentamicin (and seek advice)
Aspiration or Hospital Acquired Pneumonia (non-severe)	Co-trimoxazole (+metronidazole if aspiration suspected)
Infective Exacerbation of COPD	Doxycycline
Peritonitis/Biliary Tract/Intra-abdominal Infections	
Severe	IV Vancomycin + metronidazole +gentamicin (and seek advice)
Step down to oral	Cotrimoxazole
Skin Infections	
Cellulitis (see separate protocol)	Doxycycline
Animal bites	Metronidazole + doxycycline
Surgical Prophylaxis	See separate protocol

(Micromedex)
Effective
Benzylpenicilloyl Polylysine - Allergy to penicillin; Diagnosis Adult, Pediatric
Doxycycline Calcium Actinomycotic infection - Allergy to penicillin Adult, Pediatric.
Allergy to penicillin - Clostridial infection Adult, Pediatric
Allergy to penicillin - Listeriosis Adult, Pediatric.
Allergy to penicillin - Necrotizing ulcerative gingivitis, acute Adult, Pediatric
Allergy to penicillin - Syphilis, Primary, secondary, or early latent Adult, Pediatric
Allergy to penicillin - Yaws Adult, Pediatric.

Erythromycin Allergy to penicillin - Rheumatic fever; Prophylaxis Adult, Pediatric

Erythromycin Stearate Allergy to penicillin - Primary syphilis Adult, Pediatric Allergy to penicillin - Rheumatic fever; Prophylaxis Adult, Pediatric

Minocycline Hydrochloride Allergy to penicillin – Bacterial infectious disease Adult, Pediatric

Tetracycline Hydrochloride Allergy to penicillin - Late latent syphilis, or latent syphilis of unknown duration Adult
Allergy to penicillin - Syphilis, Primary, secondary, or early latent Adult

Evidence favours efficacy
Doxycycline Hyclate Allergy to penicillin - Meningococcal infectious disease Adult, Pediatric.

Erythromycin Lactobionate Allergy to penicillin - Female gonococcal pelvic inflammatory disease Adult, Pediatric.

Tetracycline Hydrochloride Allergy to penicillin - Anthrax Adult, Pediatric.

Allergy to penicillin - Late latent syphilis, or latent syphilis of unknown duration Pediatric
Allergy to penicillin - Syphilis, Primary, secondary, or early latent Pediatric

2. Nsaid Induced Allergy Including Aspirin
The ingestion of NSAIDs can give rise to several allergic and "pseudo allergic" reactions, which develop within minutes to hours of administration. Allergic reactions are abnormal immunologic reactions to NSAIDs, while pseudo allergic reactions are no immunologic reactions that are believed to result from acquired alterations in the biochemical pathways upon which NSAIDs act. Symptoms include rhino conjunctivitis, bronchospasm, urticaria/angioedema, and anaphylaxis. Frequent use of non-steroidal anti-inflammatory drugs (NSAIDs) has been paralleled by increasing occurrence of adverse reactions, which vary from mild local skin rashes or gastric irritation to severe, generalized symptoms and even life-threatening anaphylaxis. Symptoms include rhino conjunctivitis, bronchospasm, urticaria/ angioedema, and anaphylaxis

Pseudo allergic reactions –These are nonimmunologic reactions that are related to the cyclooxygenase-1 (COX-1)-inhibiting properties of the drug. Pseudoallergic reactions are elicited by any cyclooxygenase-1 (COX-1)-inhibiting NSAID and the likelihood that an NSAID will cause these in a susceptible patient is related to the strength with which that drug inhibits COX-1. Pseudoallergic reactions are usually seen in patients with one of the following comorbidities: the combination of asthma and chronic rhinosinusitis with nasal polyposis or chronic urticaria.

Allergic NSAID reactions- are presumed to be immunoglobulin E (IgE)-mediated immunologic reactions based upon their clinical characteristics. These are elicited by a single NSAID in a susceptible individual. Or rarely by more than one agent with similar molecular structures. Patients with allergic reactions to an NSAID have had at least one prior exposure to the culprit drug, which presumedly sensitizes them and results in symptoms upon repeat exposure to the same drug. These reactions immunoglobulin E (IgE)-mediated, and the allergen is thought to be a drug metabolite bound to a carrier protein.

NSAID reactions can be challenging to diagnose because

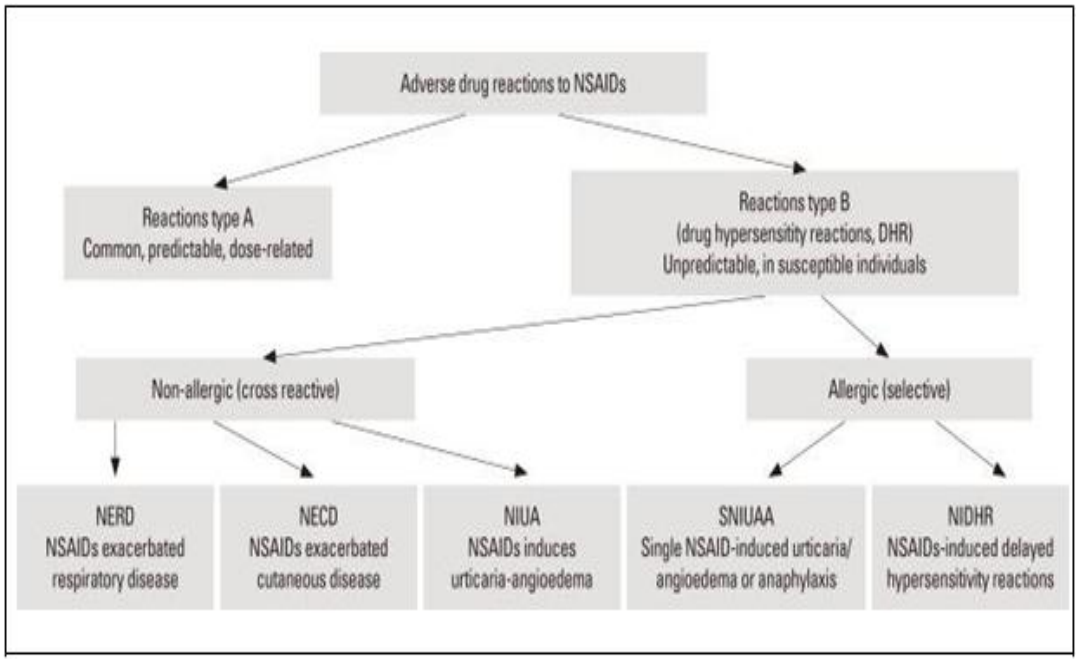
the various types of reactions can have overlapping signs and symptoms. Referral to an allergist/immunologist with expertise in drug allergy is recommended if the reaction was severe or life threatening. The presumptive diagnosis of an allergic or pseudoallergic reaction to an NSAID is based upon the historical details of the reaction(s) and the presence of certain underlying conditions. It is critical to determine if the patient has taken other NSAIDs since the initial reaction and whether the other drugs caused symptoms.

The type of NSAID reaction (ie, pseudoallergic or allergic) determines the possible management options. If the symptoms of the reaction were severe and the type of reaction is uncertain, then the patient should avoid all NSAIDs until further evaluation can be performed.

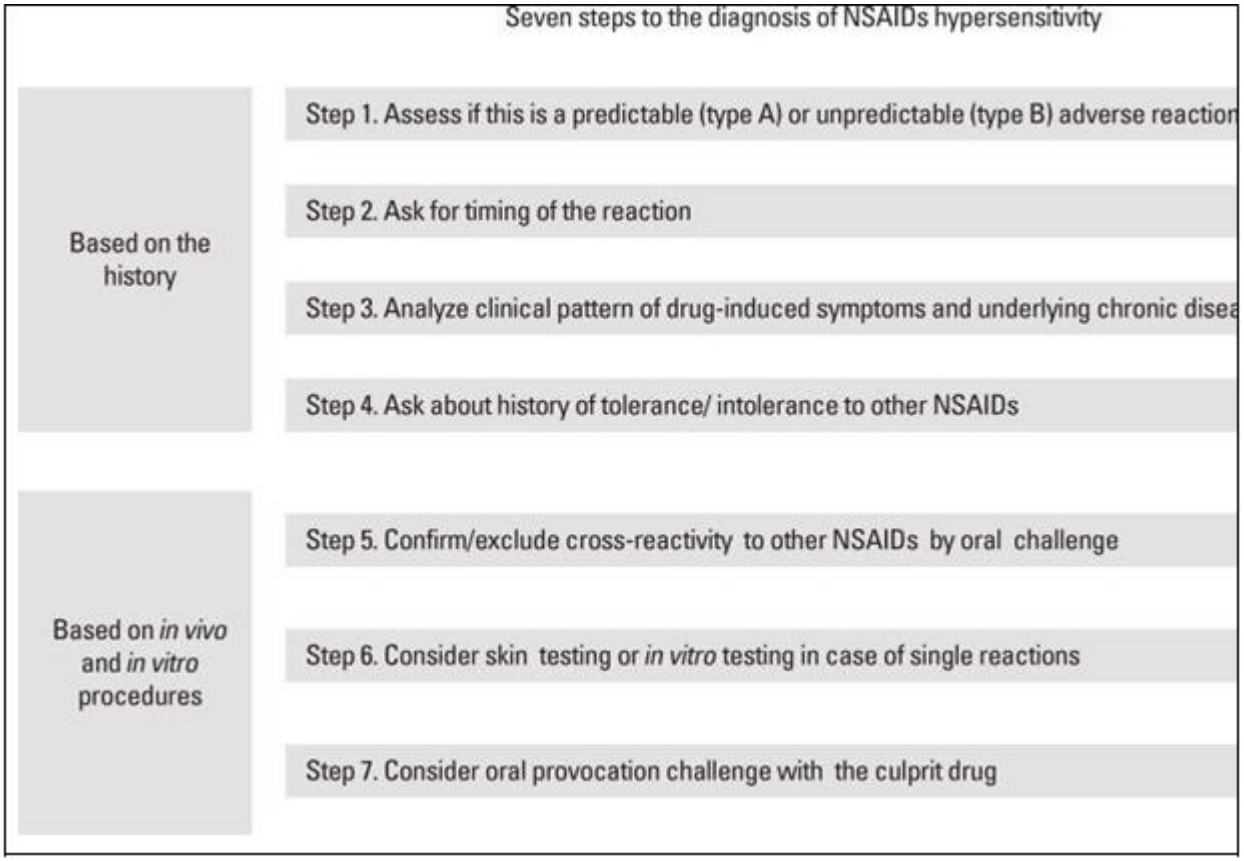
Understanding the mechanism of pharmacological activity, potency, and selectivity in inhibition of COX1/COX-2 of different NSAIDs as well as structural diversity is crucial for a proper diagnosis of NSAID-induced reactions

Classification of NSAIDs according to chemical structure

Group	**Drugs**
Salicylic acid derivates	Acetylsalicylic acid (Aspirin)
	Sodium salicylate
	Diflunisal
	Salicylsalicylic acid
	Sulfasalazine
	Olsalazine
Para-aminophenol derivatives	Acetaminophen
Indol and indene acetic acid	Indomethacin
	Sulindac
	Etodolac
Heteroaryl acetic acid	Ibuprofen
	Neproxen
	Flurbiprofen
	Ketoprofen
	Fenoprofen
Group	**Drugs**
	Oxaprozin
Anthranilic acid (fenemates)	Mefenamic acid
	Meclofenamic acid
Enolic acid derivatives (oxicams)	Piroxicam
	Tenoxicam
	Meloxicam



Classification of NSAID-induced hypersensitivity reactions				
Type of Reaction	**Name of reaction**	**Abbreviati on**	**Definition**	**Previously used names**
Cross-reactive – non allergic	NSAIDs exacerbated	NERD	Reaction manifesting primarily as bronchial	Aspirin triad, asthma triad,
Type of Reaction	**Name of reaction**	**Abbreviati on**	**Definition**	**Previously used names**
Non-immunologicall y mediated reactions)	respiratory disease		obstruction, dyspnea and nasal congestion/ rhinorrhea, occurring in patients wit an underlying chronic airway respiratory disease (asthma/ rhinosinusitis / n asal polyps).	Samter's syndrome, Widal syndrome, aspirin-induced asthma or aspirin-sensitive rhinosinusits/asth ma syndrome, aspirin-intolerant asthma, aspirin- exacerbated respiratory disease
	NSAIDs exacerbated cutaneous disease	NECD	Reaction manifesting as wheals and/or angioedema occurring in patients with a history of chronic spontaneous urticaria.	aspirin-induced urticaria; aspirin- exacerbated cutaneous disease
	NSAIDs induced urticaria- angioedema	NIUA	Reaction manifesting as wheals and/or angioedema occurring in otherwise healthy subjects (without history of chronicspontaneous urticaria). Symptoms are induced by at least two NSAIDs with different chemical structure (not belonging to the same	aspirin-induced urticaria; multiple drug-induced urticarial angioedema
Type of Reaction	**Name of reaction**	**Abbreviati on**	**Definition chemical group).**	**Previously used names**
Selective- allergic (Immunologica Lly mediated reactions)	Single NSAID-induced urticaria/angioede ma or anaphylaxis	SNIUAAA	Immediate hypersensitivity reactions to a single NSAID or to several NSAIDs belonging to The same chemical group, manifesting as urticaria, angioedema and/or anaphylaxis. These subjects tolerate other chemically non-Related NSAIDs, and usually do not have a History of chronic urticaria or asthma.	Single drug- induced reactions, allergic reactions
	NSAIDs-induceddelayedhypers ensitivityreactions	NIDHR	Reactions to a single NSAID developing more than 24 hours after drug administration and Manifesting by either Skin symptoms (exanthema, fixed drug eruption), other organ specific symptoms (e. g. renal, pulmonary) or Severe cutaneous Adverse reactions (SCAR).	



Managment

The presence of the cross-reactive or selective type of hypersensitivity has serious implications for patient's management and thus should be confirmed by oral challenge tests. If a patient previously reacted to NSADs other than aspirin, oral challenge with aspirin is the gold standard. A positive response to aspirin will confirm and n exclude the cross-reactive type of hypersensitivity. If aspirin is the culprit drug, the patient should be challenged with an alternative strong COX-1 inhibitor, and the conclusions are the same as the above, depending on a positive or negative challenge result

If the cross-reactive type of hypersensitivity (NERD, NECD, and NIUA) is diagnosed and documented, the patient is prompted to avoid all NSAIDs with strong COX-1 inhibitory activity, but selective COX-2 inhibitors can be recommended if anti-inflammatory treatment is indicated. In the case of the selective (allergic) type of hypersensitivity (SNIUAA, SNIDHR), a patient would usually react to a single drug, and thus other NSAIDs, even potent COX-1 inhibitors, may be well tolerated

Patients with pseudoallergic reactions to NSAIDs (types 1 to 4) have following options.

- Administration of acetaminophen (paracetamol) at doses no higher than 650 mg per dose.
- Administration of moderate doses of an NSAID that weakly inhibits COX-1, such as salsalate, choline magnesium trisalicylate, or diflunisal.
- Administration of a highly selective COX-2-inhibiting NSAID, such as celecoxib or Etoricoxib. This option is appropriate for patients who need a stronger NSAID or have gastrointestinal intolerance to standard NSAIDs.
- Referral to an allergy specialist for possible NSAID desensitization.

3. Sulfonamide Allergy

Sulfonamides are drugs carrying the SO2-NH2 group and are divided into 3 types based on the chemical structure: sulfonylarylamines, non-sulfonylarylamines, and sulfonamide-moiety- containing .This chemical entity is present in many different drugs of allergenic relevance are antibacterial sulfonamides (sulfamethoxazole [SMX], sulfadoxine, and sulfapyridine, which are derivates of sulfanilamides. Sulfanilamide's are characterized by a sulfonamide moiety directly attached to a benzene ring, which carries an unsubstituted amine (−NH2) at the N4 position.

The mechanism of sulfanilamide hypersensitivity reactions involves IgE, occasionally IgG, and different types of T cell–mediated reactions.

Because immune reactions are directed to the structural component, patients with an allergy to a sulfanilamides might cross-react with other sulfanilamides with a different side chain but not with sulfonamides in general. Laboratory analysis of T-cell reactions and clinical data show that non-sulfanilamide drugs, such as

glibenclamide, furosemide, and celecoxib, are not stimulatory and tolerated by patients allergic to sulfanilamides.

Sulfasalazine, which was the relevant component in our patient, is split in the gastrointestinal tract into 5-aminosalyclic acid and sulfapyridine. Importantly, a patient with an SMX allergy should avoid sulfasalazine, and patients who react to sulfasalazine should never again obtain an antibacterial sulfonamide.

Under treatment with sulfonamide antimicrobial agents, approximately 2% of the general populations have adverse drug reactions suggestive of an allergic mechanism. True allergic reactions of the anaphylactic type (IgE-mediated urticaria and anaphylaxis) are rather rare, as are IgG antibody–mediated reactions (mainly hemolytic anemia).

Cotrimoxazole was widely used in prevention and treatment of opportunistic infection in HIV-positive patients. The prevalence of rashes is higher than in the general population.

Protease inhibitors in HIV therapy.-Two sulfanilamide (amprenavir und fosamprenavir) are used as they induce a high degree of rashes (19% to 29%), which in 1% to 3% of treated persons cause a stop of therapy. Desensitization has been described

Sulfanilamide allergies include potentially life-threatening reactions, such as SJS/TEN and DRESS, which is also called drug (induced) hypersensitivity syndrome (DHS or DiHS), because not all patients have eosinophilia. It appears typically after a 2- to 10-week drug exposure. Skin rash, fever, lymph node swelling, hepatitis, or involvement of other organs clinically characterizes it. Many patients have facial swelling; some have signs of a capillary leak syndrome, probably related to the excessively high cytokine values observed during the acute disease.

Sulphonamide Antibiotic Allergy in Patient Who is HIV-Positive-Prophylaxis and treatment of Pneumocystis jiroveci pneumonia may be complicated in patients with AIDS who have a history of drug reaction allergies to sulphonamides.

Some patients may be able to tolerate cutaneous adverse effects without discontinuation of therapy and in some cases interruption of therapy or lower doses may be helpful; however, discontinue use of the sulfonamide if any of the following conditions occurs

- Rash or fever for longer than 5 days
- Absolute neutrophil count of less than 500/mcL
- Hypotension or dyspnea
- Blistering, desquamation of the skin, or mucous membrane involvement

Alternative treatment/prophylaxis options may include dapsone (contains a sulfonamide- moiety), pentamidine, atovaquone, clindamycin-primaquine, and trimetrexate-leucovorin.

Sulfasalazine Allergy in Patients with Inflammatory Bowel Disease, Ulcerative Colitis, or RheumaticDisease Sulfasalazine is a sulfonamide prodrug of 5-aminosalicylic acid with a manufacturer contraindication for use in patients with hypersensitivity to the drug or any sulfonamides. Other preparations of 5-aminosalicylic acid are available and may be preferable for use. Immunomodulatory therapies are also available

Diuretics in Patients with A Non-antibiotic Sulphonamide Allergy Several studies did not find evidence of cross-reactivity in patients with documented sulfa allergy who were treated with loop diuretics (ie, furosemide) or acetazolamide. However, some diuretics are independently associated with hypersensitivity reactions and risks of cross-reactivity are not well understood for agents that contain sulfur moieties of various types. Ethacrynic acid is the only loop diuretic that is not a sulfonamide, but availability has sometimes been a problem and ototoxic adverse effects are a concern. Graded-dose challenges or desensitization protocols are available for furosemide and torsemide.

Opioid Allergy

True IgE-mediated hypersensitivity to opioids is rare and many reactions are due to direct mast cell degranulation. Opioid drug provocation testing (DPT) is the gold standard for diagnosis but is underutilized. True IgE-mediated immediate hypersensitivity reactions are rare. Some studies implicate opioids in around 2% of cases of perioperative anaphylaxis, but this is likely to be an overestimate due to the lack of validated testing methods. An incorrect diagnosis of allergies may lead to delays in treatment and unnecessary drug avoidance.

Virtually all opioid analgesics, but particularly the naturally occurring and semi-synthetic compounds, cause histamine release as a pharmacologic effect, which may be responsible in part for reactions such as urticarial, pruritus, hypotension and flushing.5These reactions to the release of histamine are not allergic or anaphylactic in nature. Contact dermatitis and systemic hypersensitivity have also been reported.

Adverse reactions experienced from opioids can be divided into three categories, as summarised below and in Table.

Common adverse effects	Pseudo-allergic reaction	True allergic reaction
Nausea, vomiting	Mild itching, sneezing	Difficulties in breathing, swallowing and/or speaking
Constipation	Flushing	Cutaneous reactions (other than hives, e.g. maculopapular rash)
Drowsiness, delirium	Hives, redness	Angioedema/swelling of lips, tongue, face or mouth
Urinary retention	Sweating	Severe hypotension
Respiratory depression	Mild hypotension	

Unfortunately, differentiating between the three types of reactions remains a complex issue for healthcare providers, The concept of 'relative potency' is important to consider when selecting opioids for patients who experience pseudo-allergic symptoms. The frequency of pseudo-allergic reactions is dose-dependent; when the opioid dose is higher its concentration is higher in the mast cells, and there is a greater likelihood of histamine release. Therefore, these pseudo-allergic reactions are most commonly associated with low potency opioids, such as morphine and codeine, as higher doses are required to produce a therapeutic effect.

In patients who report pseudo-allergic opioid symptoms (Table), there are several options available instead of complete avoidance.

These include

1. Continuing the opioid with close monitoring and/or the addition of an antihistamine. Note: Co-administration with such adjuncts does not prevent true allergic reactions such as anaphylaxis
2. Considering a dose reduction where tolerable
3. Switching to a different opioid, even within same structural class, as shown in Table 3, or

Switching to a more potent opioid which is less likely to release histamine.

In patients who recall having symptoms that describe a true allergy (Table 1), caution should be exercised to avoid the offending drug and consider the following possible options:

- Opioids the patient has taken safely in the past
- Trialling an opioid from a different structural class to the offending agent (as shown in Table 3) and monitor closely, and/or
- Consult an immunologist for further diagnosis and management.

Relative Potency of opioids

Most Potent	Sufentanil
↑	Fentanyl
	Remifentanil
	Alfentanil
	Hydromorphone
	Methadone
	Oxycodone
	Morphine
	Codeine
	Pethidine
Least Potent	Tramadol

There are three structural classes of opioid analgesics: diphenylheptanes, phenanthrenes, and phenylpiperidines as outlined in Table The risk of cross-reactivity can be reduced if an opioid from a different structural class is used. However; it is important to note this does not eliminate the risk of an allergic reaction, as some patients may be allergic to more than one class of opioid. Therefore it is prudent these patients are monitored carefully.

Structural Class	Agents	
Diphenylheptanes	Methadone	Propoxyphene Dextropropoxyphene
Phenanthrenes "Morphine group"	Buprenorphine Hydromorphone Pentazocine	Codein Morphine Oxycodone
Phenylpiperidines	Fentanyl Alfentanil Pethidine	Remifentanil Sufentanil
Other	Tramadol	

Knowledge of opioid metabolism pathways can be valuable when distinguishing between pseudo-allergic and true allergic symptoms, and when choosing an alternative opioid that is unlikely to cause cross-reactivity. For example; as codeine is metabolised to morphine, patients with a morphine allergy should also avoid codeine. Conversely, patients who report an allergy to codeine but can tolerate morphine are unlikely to have a true allergy

Structurally opioids are categorized in to different classes as follows

- **Group 1 (aka opiates) -** Naturally occurring agents derived from the opium plant

The naturally occurring and semi-synthetic compounds appear to be the most potent histamine releasers and therefore might be the most likely to elicit or aggravate asthmatic attacks Eg:Morphine, codeine, thebaine

- **Group 2 - Semi-synthetics**

Hydrocodone, oxycodone, hydromorphone, oxymorphone, buprenorphine (heroin is also in this

group).

- **Group 3 - Synthetics**

Fentanyl (alfentanil, sufentanil, etc.), methadone, tramadol, propoxyphene, meperidine

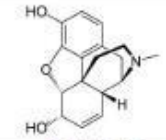
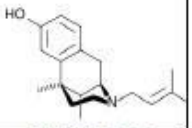
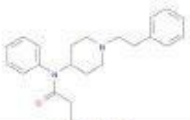
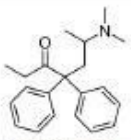
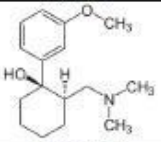
Management

Alternative analgesics such as paracetamol or NSAIDs should be considered.

Based upon theoretical considerations, a patient who continues to need an opioid after demonstrating a true allergy to morphine or a semi-synthetic opioid a trial of a synthetic opioid may be considered. Patients should be monitored carefully if an agent from another class is substituted.

Co-administration of an anti-histamine or glucocorticoid may be considered

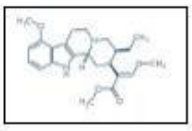
Chemical Classes of Opioids

PHENANTHRENES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLHEPTANES	PHENYLPROPYL AMINES
				
MORPHINE	PENTAZOCINE	FENTANYL	METHADONE	TRAMADOL
Buprenorphine* Butorphanol* Codeine Dextromethorphan* Dihydrocodeine Heroin (diacetyl-morphine) Hydrocodone* Hydromorphone* Levorphanol* Methylnaltrexone** Morphine (Opium, conc) Nalbuphine* Naloxone* Naloxegol* Naltrexone** Oxycodone* Oxymorphone*	Diphenoxylate Loperamide Pentazocine	Alfentanil Fentanyl Meperidine Remifentanil Sufentanil **Illicit Fentanyl** Furanyl fentanyl Acetyl fentanyl Fluoro-fentanyl Carfentanil	Methadone Propoxyphene	Tapentadol Tramadol
CROSS-SENSITIVITY RISK				
PROBABLE	POSSIBLE	LOW RISK	LOW RISK	LOW RISK

*Agents lacking the 6-OH group of morphine, possibly decreases cross-tolerability within the phenanthrene group
**6-position is substituted with a ketone group and tolerability is similar to hydroxylation

Jeffrey Fudin, BSPharm, PharmD, DAIPM, FCCP, FASHP, FFSMB
http://paindr.com/wp-content/uploads/2018/02/Opioid-Structural-Classes-Figure_-updated-2018-02.pdf

Mitragynine (Kratom)



4. Hypersensitivity reactions to fluoroquinolones

Although fluoroquinolones (FQs) are generally well-tolerated antibiotics, increasing numbers of hypersensitivity reactions have been reported. Their consumption is increasing, particularly derivatives like ciprofloxacin (CIP) and more recently moxifloxacin (MOX). This has led to an increase in allergic reactions and they are now the non-beta lactam antibiotics most frequently involved in allergic drug reactions. Most of these reactions are thought to be IgE-mediated, being anaphylaxis and urticarial the most frequently reported.

The two most common types of hypersensitivity reactions to fluoroquinolones are:

Delayed-onset maculopapular cutaneous eruptions-Mediated by drug-specific T cells

Cross-reactivity among the fluoroquinolones for this type of reaction appears to be low

For patients who require fluoroquinolone therapy in the future, we suggest identifying a safe alternative using a graded challenge with a fluoroquinolone, other than the one that caused the reaction And.

Immediate reactions,

Characterized by urticarial, pruritus, flushing, angioedema, wheezing, nausea, abdominal cramping or diarrhoea, and/or hypotension.

There is evidence of cross-reactivity among fluoroquinolones in patients with immediate reactions, but no clear patterns have been distinguished.

Skin testing can be performed, and it is critical to use nonirritating concentrations of the drugs in question, since fluoroquinolones can cause irritant false-positive reactions.

Patients with anaphylaxis in the recent past (ie, <5 years) empirically avoid all fluoroquinolone. We do not perform skin testing or challenge in such patients. If a

fluoroquinolone is required in the near future, it should be administered using a desensitization protocol.

Skin testing and challenge procedures are most useful in patients who experienced relatively mild immediate reactions, such as pruritic rashes, urticaria, or angioedema or whose reactions occurred in the remote past (>5 years) and who are likely to require fluoroquinolone therapy in the future.

For patients with negative skin test results, we suggest a graded challenge be performed to confirm that the patient tolerates the drug.

For patients with positive skin test results, we suggest avoidance of all fluoroquinolones. If a fluoroquinolone is required in the near future, it should be administered using a desensitization protocol.

5. Angiotensin-converting enzyme (ACE) inhibitors Induced Allergy

Angiotensin-converting enzyme (ACE) inhibitors are the leading cause of drug-induced angioedema in the United States because they are so widely prescribed. Patients most commonly present with swelling of the lips, tongue, or face, although another presentation is episodic abdominal pain due to intestinal angioedema. Urticaria and itching are notably absent.

ACE inhibitors induce angioedema in 0.1 to 0.7 percent of recipients, with data suggesting a persistent and relatively constant risk annually.

For unclear reasons, ACE inhibitor-related angioedema occurs more commonly in black patients. Angioedema can be life threatening but more times than not its occurrence can be managed with conservative treatment measures including discontinuation of the medication and/or administration of an antihistamine. Occasionally, epinephrine and/or steroid therapy may be warranted. In a patient having experienced ACE inhibitor-related angioedema, angiotensin receptor blockers should be used cautiously if at all. If angiotensin receptor blocker therapy is being considered in a patient with prior ACE inhibitor-related angioedema, there should be some justification for the use. Such justification might include the presence of heart failure or proteinuric nephropathic states among other considerations.

Affected areas — ACE inhibitor-induced angioedema is most commonly reported to affect the lips, tongue, face, and upper airway. The intestine can also be involved, presenting as acute abdominal pain with diarrhoea or other gastrointestinal symptoms, but this presentation may be less well recognized. The reason that these particular parts of the body are more often affected is not known.

The clinical features of ACE inhibitor-induced angioedema are related to elevated levels of bradykinin, an inflammatory vasoactive peptide, which leads to vasodilation of blood vessels. Angiotensin II is also responsible for inactivating bradykinin, while ACE (kininase II) is the primary peptidase involved in the degradation of bradykinin. Bradykinin is a peptide made of nine amino acids that increases capillary permeability and acts as a potent vasodilator. In some patients, Bradykinin levels become elevated due to impaired metabolism, which leads to release of nitric oxide and prostaglandins and results in vasodilatation and hypotension.

High levels of bradykinin stimulate vasodilation, increased vascular permeability of the post capillary venules, and allows for plasma extravasation into the submucosal tissue, leading to angioedema. ACE inhibitor-induced angioedema is thought to result from defective degradation of at least three vasoactive peptides: bradykinin, des-Arg9-BK (a metabolite of bradykinin), and substance P.

Management — The primary treatments of ACE inhibitor-induced angioedema are acute airway management if the mouth or throat is involved (until the angioedema episode has resolved) and discontinuation of the drug.

Discontinue ACE inhibitor — Angioedema caused by ACE inhibitors usually resolves within 24 to 72 hours. If ACE inhibitors are continued, there is an increased and unpredictable rate of angioedema recurrence, and attacks may become more severe or life- threatening .Patients who have experienced angioedema attributed to an ACE inhibitor should never again be treated with this group of medications.

If the cause of a patient's angioedema is unclear, we would still advise discontinuation of ACE inhibitors
Patients should be counselled that angioedema can recur in the first few months after stopping an ACE inhibitor and given advice about how to proceed if symptoms develop again. A patient handout is provided.

In patients with a history of ACE inhibitor-induced angioedema, we suggest **not** avoiding angiotensin-receptor blockers (ARBs) if an ARB has advantages over other agents for that patients.

6. Anticonvulsant Drug Allergy

Hypersensitivity reactions are common adverse drug reactions (ADRs) associated with antiepileptic's Carbamazepine is one of the routinely prescribed drugs for the treatment of epilepsy. Neuropathic or differentiation pain, which occurs in post-herpetic or trigeminal neuralgia, also responds to antiepileptic such as phenytoin, carbamazepine, and gabapentin.

Aromatic anticonvulsants [phenytoin, phenobarbital (phenobarbitone) and carbamazepine] are the most frequently involved drugs for cutaneous ADRs.

Cutaneous eruptions occur in 3% of individuals who receive carbamazepine and include diffuse erythema, exanthematous rash, urticaria, purpuric petechiae, or a mucocutaneous syndrome any of which can occur from day 8 to day 16 after treatment initiation. Other dermatological adverse effects of carbamazepine include drug hypersensitivity, exfoliative dermatitis, erythroderma, erythema multiforme, and toxic epidermal necrolysis. Rare reactions include dermatomyositis, lupus erythematosis-like syndrome, eczema, photosensitivity, pustules, psoriasiform, and lichenoid reactions and Anticonvulsant hypersensitivity syndrome (AHS).

The exact mechanism of this reaction is unknown. However, suggested mechanism of adverse drug reaction (ADR) is allergic hypersensitivity. The aromatic anticonvulsants (phenytoin, phenobarbital/phenobarbitone, and carbamazepine) are metabolised to hydroxylated aromatic compounds, such as arene oxides. If detoxification of this toxic metabolite is insufficient, the toxic metabolite may bind to cellular macromolecules causing cell necrosis or a secondary immunological response. Cross-reactivity among the aromatic anticonvulsants may be as high as 75%. In addition, there is a familial tendency to hypersensitivity to anticonvulsants

Anticonvulsant Hypersensitivity Syndrome is a delayed adverse drug reaction associated with the use of aromatic anticonvulsants. It is a multi-organ syndrome, which is potentially life- threatening .Commonly observed hypersensitivity reactions are dizziness, sleeplessness (insomnia), headache, slurred speech, nausea, fever, rashes, skin reactions and hepatitis (inflammation of the liver). In case, if you experience any sort of hypersensitivity reactions following the administration of anticonvulsant drugs, medical attention should be sought immediately.

Various Treatment options for Anticonvulsant Allergy

Initially symptomatic treatment is provided to the affected individual, which is tailored appropriately at later stages. However, the offending drug should be discontinued immediately and appropriate therapy is initiated. Topical application of steroid medications and oral consumption of antihistamines are generally advised to control the symptoms associated with rashes. Treatments include antihistamines (H_1-receptor blockers), epinephrine, glucocorticords, anabolic steroids, antigonadotropic agents, and airway management, depending on the severity of the condition Individuals who have been treated for AHS should avoid anticonvulsants like, carbamazepine, phenytoin and phenobarbitone in future.

Valproic acid appears to be safer, as do the benzodiazepines and are commonly advised for individuals who have experienced an allergic reaction to general anticonvulsants. Alternatively, one of the other non-aromatic anticonvulsant drugs such as ethosuximide, gabapentin, levetiracetam, tiagabine, and topiramate can be used.

Drugs should be Avoid If Allergic to Anticonvulsants

- Carbamazepine
- Phenytoin
- Phenobarbitone
- Lamotrigine.
- Mephenytoin
- Ethosuximide
- Methsuccimide
- Clonazepam
- Clorazepate
- Diazepam
- Valproic acid
- Gabapentin
- Topiramate
- Felbamate

7. Hypersensitivity reactions to systemic glucocorticoids

Hypersensitivity reactions to systemic glucocorticoids are rare-appear to occur in ≥0.1 percent of parenteral administrations.

Pathophysiology — The allergenic moiety in glucocorticoids that is responsible for immediate reactions has not been determined. It could be part of the native molecule or a metabolite that acts as a hapten and binds to serum proteins, creating an allergenic complex.

Signs and symptoms of immediate hypersensitivity to systemic glucocorticoids include pruritus, rash, hives, angioedema, sneezing, nausea/vomiting, dyspnea, throat tightness, wheezing/bronchospasm, hypotension, and anaphylactic shock. Hypersensitivity reactions have been rarely reported following intravenous, intramuscular, intra-articular, and oral administration

Some reports suggested that renal transplant or asthmatic patients (especially those who are aspirin-sensitive) may be at higher risk.

Causative drugs — The likelihood of a specific glucocorticoid causing hypersensitivity appears to be related to the frequency with which it is used. incidence of hydrocortisoneand methylprednisolone allergy seemed higher than allergy to other glucocorticoids hydrocortisone -5% methylprednisolone- 41 % prednisolone - 20 % Triamcinolone - 14 %

Cross Reactivitry-without an allergy evaluation or challenge procedure, it is not possible to choose a "safe" alternative glucocorticoid empirically for a patient who has had an immediate reaction to a specific agent.

Some papers suggested that hydrocortisone cross-reacts

more with methylprednisolone than with a halogenated steroid, such as dexamethasone and betamethasone.
Patients with signs or symptoms of an immediate reaction to a systemic glucocorticoid should be referred to an allergy specialist whenever possible and advised to avoid systemic use of all glucocorticoids until evaluated.

Other possible allergens in glucocorticoid preparations
Succinate esters — To create soluble injectable preparations, hydrophobic glucocorticoids are attached by a chemical bond to esters, such as sodium succinate and sodium phosphate. There is some evidence to suggest that patients can be reactive to these esters, rather than to the glucocorticoid itself.

Preservatives and excipients — Glucocorticoid preparations may contain preservatives and excipients, such as lactose, carboxymethylcellulose, polyethylene glycol, or hexylene glycol. Allergic reactions to these components are possible.

For skin testing, preservative-free glucocorticoid solutions are preferred whenever possible. If a preservative-free preparation is not available and/or if a patient had an allergic reaction after receiving a glucocorticoid preparation containing a preservative, then a positive result to the preservative-containing preparation should be followed by skin testing with a preparation of the preservative (prick-puncture and if negative, intradermal).

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