



Standard Treatment Workflow (STW)

CUTANEOUS ADVERSE DRUG REACTIONS- PART A

ICD-10-L27.0

Cutaneous adverse drug reactions (cADR) are undesirable clinical manifestations to a drug, which include predictable or unanticipated side effects, with or without systemic involvement

COMMON TYPES OF cADR

NON- SEVERE cADR

Fixed drug eruption (FDE)

Maculopapular/ Exanthematous reactions

Drug induced hypersensitivity syndrome/ DRESS*

SEVERE cADR

Acute generalized exanthematous pustulosis

Angioedema/ Anaphylaxis*

Erythema multiforme/ Stevens Johnson syndrome/ Toxic epidermal necrolysis*

*Refer to separate STW on Urticaria/ Angioedema, and cADR Part-B for DRESS/ Stevens Johnson syndrome/ Toxic epidermal necrolysis

GENERAL PRINCIPLES

- **Common presentation:** Sudden onset of an itchy rash that is symmetrically distributed and spreads rapidly. May have had a previous similar allergic reaction.
- **Withdraw:** The offending drug(s) immediately, except life saving drugs (if they are not the suspected drugs)
- Take necessary measures to **prevent similar events** (record on patient's medical chart, educate, provide allergy card etc.)
- **Recognize danger signs**
 - » Mucosal lesions, purpuric lesions, skin tenderness, bullous lesions (peeling/ sloughing of skin)
 - » Systemic symptoms: High grade fever, jaundice, decreased urine output
- **Action required:** Prompt and urgent care at a specialised centre. Apart from maintenance of vitals, withdrawal of all drugs, initiation of oral or intravenous corticosteroids, care of the eye, evaluation of secondary infection/ sepsis are important

HISTORY ELICITATION

- History of prior adverse drug reaction
- Patients on polypharmacy: list all recently introduced drugs and/ or dosage increments. However, all drugs should be kept in suspect list
- Concomitant viral infection or illnesses affecting drug metabolism or excretion (eg. chronic kidney disease)

TIMELINES FOR DRUG REACTIONS AND SOME TYPICAL EXAMPLES

- **5-15 minutes:** Anaphylaxis, urticaria, angioedema
- **Few hours:** Reactivation of fixed drug eruption
- **Few hours- 2 weeks:** Maculopapular exanthem, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, first episode of FDE
- **4- 12 weeks:** DRESS syndrome, Dapsone syndrome, anticonvulsant induced hypersensitivity syndrome

1) FDE

- **Distinctive drug eruption:** usually recur at the same site on drug re-exposure
- **Acute FDE:** dusky red-violaceous plaques with or without vesiculation or bullae
- **Common sites:** lip, genitalia, proximal extremities, low back, sacrum
- **Local symptoms:** pruritus, burning, and pain; solitary or numerous (latter is difficult to differentiate from toxic epidermal necrolysis). Resolve with persistent hyperpigmentation
- **Clinical variants:** bullous, generalised, pure mucosal
- **Common drugs that cause FDE:** Sulfonamides, tetracyclines, quinolones, NSAIDs, dapsone, antimalarials, barbiturates, nitroimidazoles

REFER TO HIGHER CENTER IF

- There are atypical symptoms
- Uncertain diagnosis
- Severe reaction (multiple lesions, bullae, severe mucosal lesions, systemic symptoms)

MANAGEMENT

PRIMARY HEALTH CENTRE

- Withdraw the drug
- General management: Bullous/ moist/ oozy lesions- normal saline compresses
- Topical steroid: Betamethasone valerate cream BD for cutaneous lesions
- Antihistamines -Tab Pheniramine maleate 25 mg BD/TID for itching
- Review patient in 1 week

SECONDARY LEVEL CARE

- Continue treatment as described at primary care level
- If severe: add short course of oral steroids: Prednisolone 0.5 mg-1 mg/kg for 3-5 days

TERTIARY LEVEL

- Admit the patient if the episode is generalized and severe
- Histopathology in doubtful cases
- If the oral mucositis is severe, consider parenteral steroids
- Provocation tests may be done after resolution of symptoms (usually after 1-6 months) by an oral challenge with each suspected individual drug consecutively

2) MACULOPAPULAR/EXANTHEMATOUS REACTIONS

- Abrupt onset, erythematous maculopapular eruption
- Typically starts on the trunk, spreads symmetrically to extremities. Dependent areas may have purpuric lesions
- Usually accompanied by mild systemic symptoms- pruritus, low grade fever, mild eosinophilia
- All drugs taken in the last 4 weeks are suspects. May manifest within 48 hours if the patient has taken the drug previously
- Commonly observed with co-trimoxazole, cephalosporins, anti-tubercular drugs, aminopenicillins, quinolones, dapsone, NSAIDs, anticonvulsants, nevirapine, abacavir, allopurinol, leflunomide
- Differential diagnosis: Viral exanthem, Rickettsial rash, HIV, Kawasaki disease (in children)
- Fever and prodromal symptoms (coryza, malaise) occur before the development of rash in most viral exanthems and the drug history is usually negative prior to it

RED FLAG SIGNS

- Mucosal involvement
- Purpuric lesions
- Bullous lesions
- Skin tenderness
- Facial/ acral edema
- Erythroderma
- Systemic symptoms - High grade fever, hepatitis, renal involvement, significant eosinophilia

MANAGEMENT

PRIMARY CARE

- Withdraw the suspect drug(s)
- Pheniramine maleate 25 mg TID
- Calamine lotion
- Refer to higher center if symptoms persist or red flag signs present

SECONDARY CARE

- Confirm the diagnosis by history and clinical findings
- Admit if red flag signs are present
- Laboratory tests: CBC (Eosinophilia supports the diagnosis), LFT, serum creatinine, urine M/E
- Treatment: in severe cases, prednisolone 0.5-1 mg/ kg/ day x 5-7 days (after ruling out infection)

TERTIARY CARE

- Admit if red flag signs are present
- Confirm diagnosis of drug rash
- Additional lab tests if required: ANA, HIV, skin biopsy
- Consider DRESS if rash is progressing or significant organ involvement is evident

DRUG PROVOCATION TEST

In the absence of any reliable *in vitro* test in clinical setting, oral drug challenge is the only way to detect the responsible drug

Usually undertaken when drug avoidance is impractical, especially in case of polypharmacy or life saving medicines (e.g. antituberculous therapy)

- Take a written consent prior to challenge
- Contraindicated in active illness or pregnancy
- Assess the risk benefit ratio
- Caution: patients on antihistamines, oral steroids and tricyclic antidepressants may have a modified response to the challenge
- A negative test only indicates that the patient is not allergic to the drug at the time of challenge
- The dose of drug for challenge depends on the severity of the previous reaction and the pharmacokinetic profile

- Drug provocation should always be done
 - After admission/ under observation except in cases with FDE
 - Usually in the daytime so that the faintest erythema is appreciated
 - It should be treated immediately and aggressively with an appropriate dose of systemic corticosteroid which may be required for only 1-2 days
 - Drug provocation in cases with DRESS has to be avoided or if provoked, a prolonged retreatment is required
 - In case of SJS-TEN drug provocation should be done only if the drug cannot be avoided. Provocation is preferred with a chemically unrelated molecule
- Intradermal tests can be done in IgE mediated reactions
- Patch test has a low sensitivity and should not be relied upon in severe cADR



FDE



BULLOUS FDE



MACULOPAPULAR RASH

