STANDARD TREATMENT WORKFLOW (STW)

Cutaneous Adverse Drug Reactions – Part A

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Standard Treatment Workflow (STW)

Cutaneous Adverse Drug Reactions (cADR)

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<th>COMMON TYPES OF cADR</th>
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*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
  ▶ Muscular lesions, purpura lesions, skin tenderness, bullous lesions (peeling/soughing of skin)
  ▶ Systemic symptoms: High grade fever, jaundice, decreased urine output

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 illness affecting skin

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

**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.
- **Pruritus**: Begins immediately, except life-saving drugs (if they are not the suspected drugs).
- **Location of rashes**: Common sites: (a) genitalia, proximal extremities, low back, sacrum.
- **Local symptoms**: pruritus, burning, and pain persist or are numberous (later is difficult to differentiate from toxic epidermal necrolysis). Resolve with persistent hyperpigmentation.
- **Clinical variants**: bullous, generalized, purpura, mucositis.
- **Common drugs that cause ADRs**: phenobarbitone, tetracyclines, quinolones, NSAIDs, dapsone, antimalarials, barbiturates, nitrofurantoins.

**HISTORY ELUCIDATION**

- **History of prior drug reaction**: Note if a drug is related to a prior reaction.
- **Location of rashes**: History of drug use, and a previous similar reaction.
- **Severity of rashes**: Progression of symptoms, severity of reaction.
- **5-15 minutes**: Anaphylaxis, urticaria, angioedema.

**TIMELINES FOR DRUG REACTIONS**

- **1-2 days**: Maculopapular exanthem, erythema multiforme, Stevens – Johnson syndrome, toxic epidermal necrolysis, first episode of DRESS.
- **4-12 weeks**: DRESS syndrome, Dapsone syndrome, anticonvulsant-induced hypersensitivity syndrome.

**TREATMENT**

- **Primary health centre**: Withdraw the drug.
- **Secondary level care**: Continue treatment as described at primary care level; if necessary, add short course of oral corticosteroids.
- **Tertiary level**: Admit the patient if the episode is generalized and severe.

**MANAGEMENT**

- **Primary**: Withdraw the suspect drug(s).
- **Secondary**: Confirm diagnosis by history and clinical findings.
- **Tertiary**: Admit if red flag signs are present.

**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**.
- **Drugs provocation should be impractical, especially in case of polypharmacy**.
- **After admission/under observation except in cases with FDE**.
- **Usually in the daytime so that the fastest ophthalmia is appreciated**.
- **Should be treated immediately and aggressively with an appropriate dose of systemic corticosteroids which may be required for only 1-2 days**.
- **Drug provocation in cases with DRESS has to be avoided or if provoked, a prolonged treatment is required**.
- **In cases of SJS-TEN drug provocation should be done only if the drug cannot be avoided**.
- **Consider a trial of prednisolone with a chemically unrelated molecule**.
- **Intradermal tests can be done in SJS/TEN mediated reactions**.
- **Patch test has a low sensitivity and should not be relied upon in severe ADR**.

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**Standard Treatment Workflow (STW)**

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

**Common Types of ADRs**

- **Non-severe ADRs**
  - Fixed drug eruption (FDE)
  - Maculopapular/Exanthematous rash
  - Drug-induced hypersensitivity syndrome (DRESS)
- **Severe ADRs**
  - Acute generalized exanthematous pustulosis
  - Angioedema/Anaphylaxis
  - Erythema multiforme

**Primary Health Centre**

- Withdraw the drug.
  - General management: Buluous/moist/ozy lesions: normal saline compresses.
  - Topical steroid: Betamethasone valerate cream.
  - Antihistamines: Tab. Pheniramine maleate 25 mg BD/TO for 3 days.
  - Review patient in 1 week.

**Secondary Level Care**

- Continue treatment as described at primary care level.
- If severe: Add short course of oral corticosteroids.
- Discontinue: Prednisolone 30 mg/1 mg/ml for 3-5 days.

**Tertiary Level**

- Admit the patient if the episode is generalized and severe.
- Histopatolgy in doubtful cases.
- If oral mucositis is severe, consider parenteral steroids.
- Provocation tests may be done after resolution of symptoms (usually after 1-4 months) by oral challenge with each suspected individual drug consecutively.

**Maculopapular Exanthematous Rashes**

- Abrupt onset, erythematous maculopapular eruption.
- Typically starts on the trunk, spreads symmetrically to extremities. Dependent areas may have purpuric lesions.
- Occasionally accompanied by mild systemic symptoms: pruritus, low-grade fever, mild eosinophilia.
- All drugs taken in the last 4 weeks are suspect. May manifest within 48 hours if the patient has taken the drug previously.
- Commonly observed with: trimethoprim-sulfamethoxazole, erythromycin, oral contraceptives, diuretics, minocycline, dapsone, NSAIDs, anticonvulsants, nevirapine, naproxen, abacavir, allopurinol, leflunomide.
- Differential diagnosis: Viral exanthem, eczematous rash, HIV, Kawasaki disease (in children).
- Fever and prodromal symptoms (cough, malaise) occur before the development of skin rash.

**Red flag signs**

- Maculopapular rash.
- Bullous lesions.
- Erythema nodosum.
- Erythema multiforme.
- Systemic symptoms: High-grade fever, hepatitis, renal involvement, significant eosinophilia.

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**Dapsone Syndrome**

- Fever and rash.
- No history of prior drug reaction.
- No local symptoms.
- No systemic symptoms.

**Bullous Drug Reaction**

- Fever.
- Swollen, red skin.
- No local symptoms.
- No systemic symptoms.

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**Reference**

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