TABLE 74-3 CLINICAL FEATURES OF SEVERE CUTANEOUS DRUG REACTIONS

Diagnosis	Mucosal Lesions	Typical Skin Lesions	Frequent Signs and Symptoms	Alternative Causes Not Related to Drugs
Stevens-Johnson syndrome	Erosions usually at two or more sites	Small blisters on dusky purpuric macules or atypical targets; rare areas of confluence; detachment ≤10% of body surface area	Most cases involve fever	10–20% cause not determined
Toxic epidermal necrolysis[a]	Erosions usually at two or more sites	Individual lesions like those seen in Stevens-Johnson syndrome; confluent erythema; outer layer of epidermis separates readily from basal layer with lateral pressure; large sheet of necrotic epidermis; total detachment of >30% of body surface area	Nearly all cases involve fever, "acute skin failure," leukopenia	10–20% cause not determined
Hypersensitivity syndrome	Infrequent	Severe exanthematous rash (may become purpuric), exfoliative dermatitis, facial edema	30–50% of cases involve fever, lymphadenopathy, hepatitis, nephritis, myocarditis, eosinophilia, atypical lymphocytes	Cutaneous lymphoma
Acute generalized exanthematous pustulosis	About 20% erosions (mouth, tongue)	Initially nonfollicular, small pustules overlying edematous erythema, sometimes leading to superficial erosions	Fever, burning, pruritus, facial swelling, leukocytosis, hypocalcemia	Infection
Serum sickness or reactions resembling serum sickness	Absent	Morbilliform lesions, sometimes with urticarial plaques (typically polycyclic)	Fever, arthralgias	Infection
Anticoagulant-induced necrosis	Infrequent	Erythema then purpura and necrosis, especially of fatty areas	Pain in affected areas	Disseminated intravascular coagulopathy, septicemia
Angioedema	Often involved	Urticaria or swelling of central part of face	Respiratory distress, cardiovascular collapse	Insect stings, foods

[a]Overlap of Stevens-Johnson syndrome and toxic epidermal necrolysis have features of both and attachment of 10–30% of body surface area may occur.

Source: Adapted from JC Roujeau, RS Stern: N Engl J Med 331:1272, 1994.

The decision to continue or discontinue any medication will depend on the severity of the reaction, the severity of the primary disease, the degree of suspicion of causality, and the feasibility of an alternative safer treatment. In any potentially fatal drug reaction, elimination of all possible suspect drugs or unnecessary medications should be attempted. Some rashes may resolve when "treating through" a benign drug-related eruption. The decision to treat through an eruption should, however, remain the exception and withdrawal of every suspect drug the general rule. On the other hand, drugs that are not suspected and are important for the patient (e.g., antihypertensive agents) generally should not be quickly withdrawn. This approach prevents reluctance to future use of these agents.

RECOMMENDATION FOR FUTURE USE OF DRUGS

The aims are (1) to prevent the recurrence of the drug eruption and (2) not to compromise future treatments by contraindicating otherwise useful medications.

Begin with thorough assessment of drug causality. Drug causality is evaluated based on timing of the reaction, evaluation of other possible causes, effect of drug withdrawal or continuation, and knowledge of medications that have been associated with the observed reaction. Combination of these criteria leads to considering the causality as definite, probable, possible, or unlikely. The RegiSCAR group has proposed a useful algorithm called Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN) to determine drug causality in SJS/TEN. A drug with a "definite" or "probable" causality should be contraindicated, a warning card or medical alert tag (e.g., wristband) should be given to the patient, and the drugs should be listed in the patient's medical chart as an allergy.

A drug with a "possible" causality may be submitted to further investigations depending on the expected need for future treatment.

A drug with "unlikely" causality or that has been continued when the reaction improved or was reintroduced without a reaction can be administered safely.

The usefulness of laboratory tests to determine causality is still debated. Many in vitro immunologic assays have been developed, but the predictive value of these tests has not been validated in any large series of affected patients; these tests exist primarily for research and not clinical purposes.

In some cases, diagnostic rechallenge may be appropriate, even for drugs with high rates of adverse reactions. Desensitization is often successful in HIV-infected patients with morbilliform eruptions to sulfonamides but is not recommended in HIV-infected patients who manifested erythroderma or a bullous reaction in response to their earlier sulfonamide exposure.

In patients with history suggesting immediate IgE-mediated reactions to penicillin, skin-prick testing with penicillins or cephalosporins has proved useful for identifying patients at risk of anaphylactic reactions to these agents. However, skin tests themselves carry a small risk of anaphylaxis. Negative skin tests do not totally rule out IgE-mediated reactivity, but the risk of anaphylaxis in response to penicillin administration in patients with negative skin tests is about 1%. In contrast, two-thirds of patients with a positive skin test experience an allergic response upon rechallenge.

For patients with delayed-type hypersensitivity, the clinical utility of skin tests is more questionable. At least one of a combination of several tests (prick, patch, and intradermal) is positive in 50–70% of patients with a reaction "definitely" attributed to a single medication. This low sensitivity corresponds to the observation that readministration of drugs with negative skin testing resulted in eruptions in 17% of cases.

CROSS-SENSITIVITY

Because of the possibility of cross-sensitivity among chemically related drugs, many physicians recommend avoidance of not only the medication that induced the reaction but also all drugs of the same pharmacologic class.