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# High-risk drug rashes

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**Key Messages**

- Drug rashes are common and mostly benign, but some carry high risk of morbidity and mortality.
- Early diagnosis and prompt management are essential in cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms syndrome, multiple drug hypersensitivity syndrome, acute generalized exanthematous pustulosis, and drug-induced bullous pemphigoid.
- The lack of reliable routine tests for identification of the causative agent imposes difficulty in patients receiving multiple medications.
- In addition to immediate discontinuation of use of the suspected drug(s), management is basically monitoring of vital organ functions and individualized supportive treatment.
- Immunomodulatory and/or immunosuppressant agents may be judicially used as guided by published studies.

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ABSTRACT

**Objective:** To provide a brief overview of the clinical presentation, common offending agents, management, prognosis, and mortality of 6 selected high-risk drug rashes, namely, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, multiple drug hypersensitivity (MDH) syndrome, acute generalized exanthematous pustulosis (AGEP), and drug-induced bullous pemphigoid (DIBP).
**Data Sources:** A review of the published literature was performed with PubMed and supplemented with our clinical experience.
**Study Selections:** The most recent clinically relevant studies and older seminal works were selected.
**Results:** Most of the published data on these uncommon rashes were based on small observational series or case reports. SJS and TEN have specific genotypes association with certain drugs, have high morbidity and mortality, and require aggressive management by a team of multiple specialists. DRESS syndrome is a severe, prolonged multiorgan reaction, yet it has a better prognosis than TEN. MDH is a syndrome of repeated reactions to unrelated drugs that often imposes diagnostic and management difficulties. AGEP consists of generalized sterile small pustules, usually mistaken for infection with subsequent inappropriate treatment. Bullous pemphigoid presents with tense pruritic bullae and characteristic linear basement membrane deposition of IgG and C3. DIBP has much better prognosis than the autoimmune variety.
**Conclusion:** In such high-risk drug rashes, early recognition, immediate withdrawal of the suspected drug(s), prompt individualized management, and monitoring of vital organs function are mandatory for reducing morbidity and mortality. The lack of reliable tests for identification of the causative agent imposes difficulty, particularly in patients receiving multiple medications.


## Introduction

The skin is the most commonly involved organ in adverse drug reactions. Most drug-induced rashes are benign and self-limited, but certain ones are signs of serious drug reactions that carry high risk of morbidity and mortality. They should be recognized early and managed promptly. This article provides a brief overview of the clinical

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presentation, common offending agents, management, prognosis, and mortality of 6 selected drug-induced rashes, namely, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, multiple drug hypersensitivity (MDH) syndrome, acute generalized exanthematous pustulosis (AGEP), and drug-induced bullous pemphigoid (DIBP).

## SJS and TEN

SJS and TEN are overlapping conditions and, for simplification, will be addressed together.

### *Clinical Presentation*

In the past, erythema multiforme (EM) was believed to be a common precedent to SJS/TEN, but now these conditions are clinically and immunopathologically considered separate entities.[1,2] EM primarily presents as targetlike skin lesions with dark necrotic centers surrounded with erythema; bullous lesions may occur as well. EM is mostly secondary to infection, particularly to human herpesvirus (HHV), whereas SJS and TEN are vastly related to drugs.[3] In general, EM is a benign condition, whereas SJS (Fig 1) and TEN (Fig 2) can be associated with serious morbidities and high mortality.

In a longitudinal observational study in the United Kingdom,[4] the estimated overall incidence of SJS/TEN was 5.76 cases per million person-years, with a peak of 8.97 in children 7 to 9 years old and another of 8.75 in elderly people (≥80 years old). No difference by sex was found, but there was a tendency of higher incidence in blacks and Asians compared with whites.

SJS and TEN symptoms usually begin within 1 to 3 weeks of drug introduction,[5,6] presenting as epidermal detachment with bullae and erosions, and mucous membrane involvement. The classification as SJS or TEN is based on the percentage of body surface area with epidermal detachment: SJS involves less than 10%, TEN involves more than 30%, and SJS/TEN overlap involves 10% to 30%.[7] Gentle rubbing of the skin close to bullae causes separation (sloughing) of the superficial layer of the skin (Nikolsky sign). The mucosal lesions are most frequently oral, conjunctival, and sometimes genital.[5] Genitourinary involvement usually causes dysuria.[6]

### *Common Offending Agents*

The most common inciting drugs in SJS/TEN are antibiotics, antiepileptic drugs, nonsteroidal anti-inflammatory drugs, and allopurinol.[6,8–10]

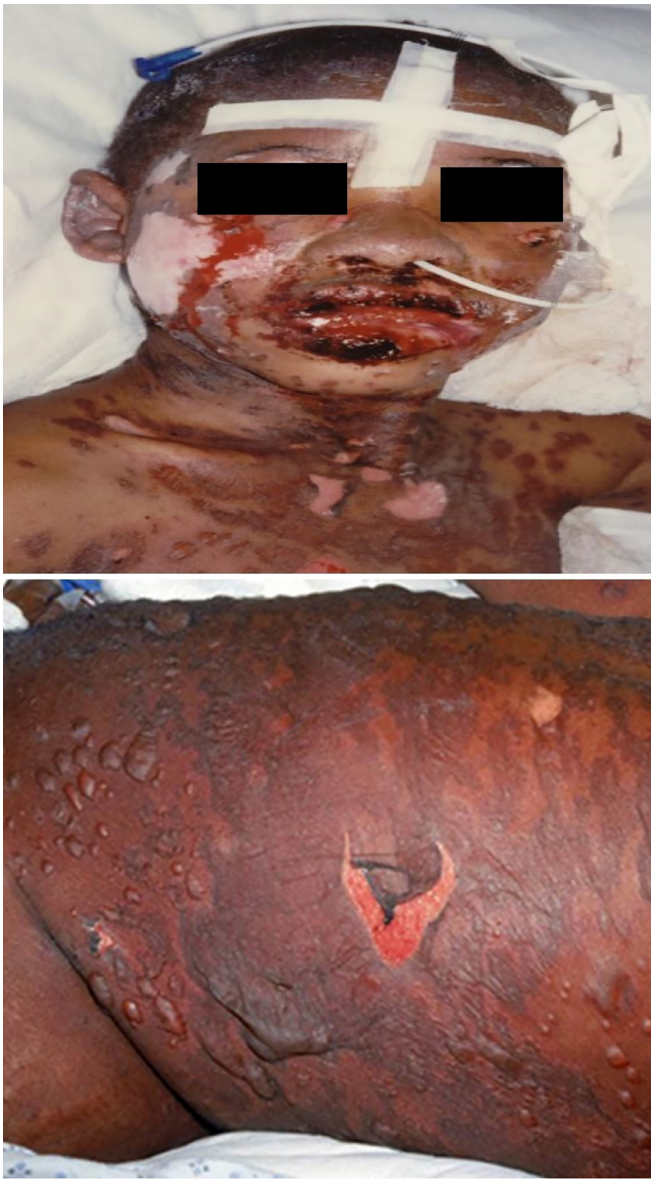

**Figure 2.** Toxic epidermal necrolysis with extensive epidermal detachment and mucosal involvement in a young girl after taking phenytoin.

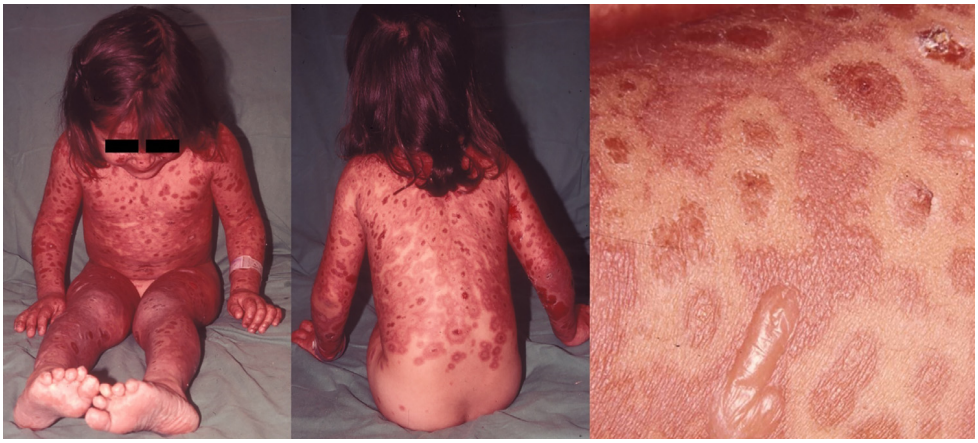

**Figure 1.** Stevens-Johnson syndrome in a 4-year-old girl after receiving thiabendazole showing extensive skin involvement with typical targetlike lesions (dark necrotic center and erythematous outer ring) and multiple bullae. She also had conjunctival involvement (not shown).

Offending antibiotics include trimethoprim-sulfamethoxazole, cephalosporins, penicillins, carbapenems, and vancomycin.[6,11]

We previously reported the case of 5 siblings (2-7 years old) who simultaneously received thiabendazole, 3 of whom developed severe generalized rashes (EM in 2 and SJS in 1).[12] HLA genotypes have been associated with adverse reactions to specific drugs. SJS/TEN reactions to carbamazepine are strongly correlated with HLA-B*15:02 in Thai, Han Chinese, Malay, and Indian populations.[13-18] The US Food and Drug Administration recommends screening patients with Asian ancestry for HLA-B*15:02 before starting carbamazepine because of the risk of SJS/TEN.[19] Oxicams (eg, meloxicam) and sulfonamides have been associated with TEN in Europeans with HLA-B*12.[20] Allopurinol-induced SJS/TEN has been associated with HLA-B*58:01 in Thai and Chinese patients.[21,22]

### *Pathogenesis*

The mechanism of SJS/TEN is most compatible with a delayed hypersensitivity reaction. The drug or a drug-peptide complex is recognized by T-cell receptors, leading to cytotoxic T-cell and natural killer cell–mediated cytotoxicity (possibly through granulysin, Fas-Fas ligand interactions, perforin, and granzyme B) and cytokine expression, including tumor necrosis factor α (TNF-α) and interferon γ (IFN-γ).[23] An in vitro study of carbamazepine-specific cytotoxic T lymphocytes from patients with HLA-B*15:02 and carbamazepine-induced SJS/TEN found that HLA-B*15:02 presented carbamazepine to cytotoxic T lymphocytes without intracellular antigen processing.[24]

Histologic analysis of EM major and early SJS/TEN found scattered necrotic keratinocytes in the lower layer of the epidermis with vacuolization at the epidermal-dermal junction. EM major involves the basal layer with prominent dermal infiltration and extravasation of erythrocytes, while displaying less epidermal necrosis than SJS/TEN. Established SJS/TEN shows extensive full-thickness keratinocyte necrosis and subepidermal bullae.[25]

### *Management*

Supportive care is the mainstay of treatment in addition to immediate withdrawal of the suspected offending medication(s). Support fluids should maintain a urinary output of 0.5 to 1.0 mL/kg per hour. Supplemental nasogastric tube feeding may be helpful to maintain adequate calorie and protein intake, especially in patients with mucosal involvement.[9] Patients should ideally be treated in a burn unit. Ocular or genitourinary involvement should prompt consultation of appropriate specialists to reduce long-term sequelae.[23] Ocular complications may occur in more than one-third of patients and include symblepharon and corneal ulceration.[9]

Corticosteroid therapy has produced conflicting results.[7,26-28] Intravenous immunoglobulin (IVIG) therapy is used with varying degrees of success.[7,29-31] The rarity of SJS/TEN makes randomized clinical trials difficult, so most data come from observational studies on small series. The combination of a corticosteroid and IVIG for 5 days seems to be associated with better survival rate than corticosteroids alone.[32] According to a retrospective medical record review, cyclosporine was associated with decreased mortality, but the number of patients was small.[33] Plasmapheresis was successful in some cases,[34] particularly in combination with cyclosporine.[35] TNF-α inhibitors, such as infliximab and etanercept, have produced promising results.[36,37] In a report on 3 severe cases, umbilical cord mesenchymal stem cell transplantation resulted in survival in all.[38] According to a meta-analysis of 96 studies on SJS/TEN treatment with various immunomodulators, corticosteroids and cyclosporine seemed to be associated with the best outcome.[28] A major limitation of such comparisons, however, is the variation among reported series regarding sample size, age, causative drug, severity of reaction, duration between onset and treatment initiation, dosage, duration, and comorbid conditions.

### *Prognosis and Mortality*

Morbidity and mortality of patients with SJS/TEN vary widely and are much higher in patients with TEN. In a recent review of patients hospitalized with SJS/TEN,[9] recovered cases showed desquamation and healing of the skin within 2 to 3 weeks (Fig 3). Nearly half of all cases had respiratory failure, leading to intubation and mechanical ventilation, and almost one-fifth had shock that required vasoactive drugs. Approximately 60% had infectious complications, including pneumonia, bacteremia, and urinary tract infections. The most common pathogenic organisms were *Pseudomonas*, *Staphylococcus*, and *Acinetobacter*. An analysis of US inpatients with SJS/TEN found that 14% required mechanical ventilation, 9% had dialysis, and 9% received artificial nutrition.[39]

Long-term sequelae among survivors can be disabling, particularly ocular complications, such as visual impairment, chronic photophobia, and dry eyes. Association with nonsteroidal anti-inflammatory drugs may be a risk for chronic ocular complications, such as conjunctival hyperemia, decreased tear volume, limbal deficiency, and symblepharon.[8] In cases with severe eye involvement, amniotic membrane graft can be sight-saving.[40,41] Oral sequelae include sicca syndrome, synechiae affecting mouth mobility, recurrent ulcers, and depapillation of the tongue. Children may have dental growth abnormalities. Airway epithelial injury can result in bronchiolitis obliterans. Pulmonary function testing may reveal alveolar diffusion impairment. Months after an acute phase that involves genital lesions, some patients develop urogenital adhesions and strictures. Esophageal strictures may also develop; more rarely, intestinal ulcerations may

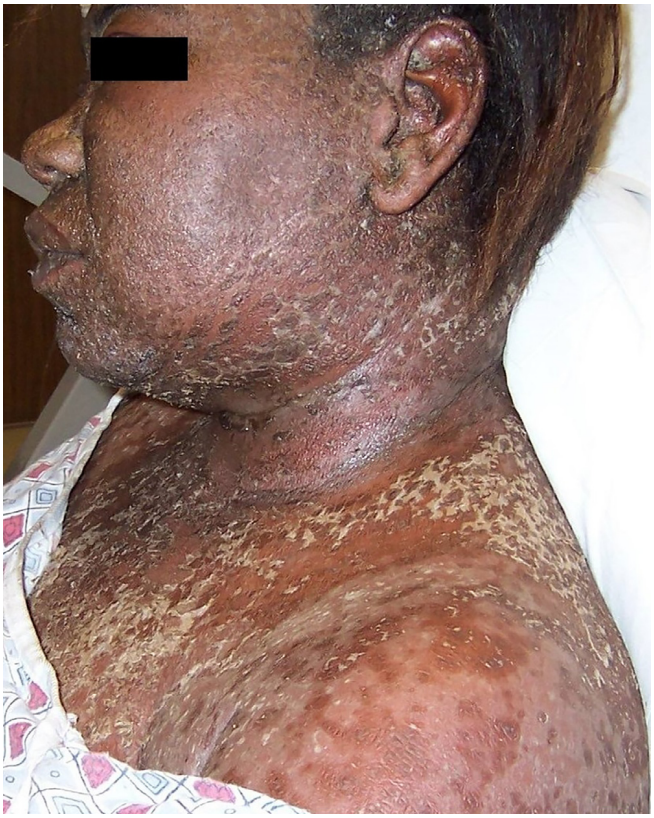

**Figure 3.** Desquamation in the healing stage of Stevens-Johnson syndrome.

**Table 1**
Score for Predicting Mortality Risk in Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SCORTEN)[a]

| SCORTEN total | Mortality rate, % | Mortality odds ratio |
|---|---|---|
| 0-1 | 3.2 | 1 |
| 2 | 12.1 | 4.1 |
| 3 | 35.3 | 14.6 |
| 4 | 58.3 | 42.0 |
| ≥5 | 90 | 270.0 |

[a]Modified from Bastuji-Garin et al.[43] Variables (each 1 point) included the following: age of 40 years or older, heart rate of 120/min or higher, concomitant malignant tumor, epidermal detachment at presentation greater than 10% of body surface area, serum blood urea nitrogen concentration greater than 10 mmol/L (>28 mg/dL), serum bicarbonate concentration less than 20 mmol/L (<20 mEq/L), and serum glucose concentration greater than 14 mmol/L (>250 mg/dL).

cause diarrhea and malabsorption. Vanishing bile duct syndrome (loss of >50% of interlobular bile ducts) can cause chronic cholestasis. Cutaneous complications include hyperpigmentation or hypopigmentation (especially in children), hypertrophic and keloid scars, shedding of nails, chronic pruritus, photosensitivity, hyperhidrosis, and heterotopic ossification.[42]

The overall mortality rate for SJS is approximately 5%, whereas TEN mortality is much higher at approximately 15% to 30%.[11,31,39] Risk factors for mortality in the United States include older age, higher number of chronic conditions, hematologic malignancy, renal failure, septicemia, pneumonia, and tuberculosis.[39] SJS/TEN caused by allopurinol also has a higher mortality.[9] A validated tool (Table 1) is used to predict mortality and the severity of illness score for TEN (SCORTEN).[43]

## DRESS Syndrome

DRESS syndrome is a severe multiorgan adverse drug reaction of delayed onset that may involve lymphocyte activation, eosinophilia, and reactivation of HHV.[44]

### *Clinical Presentation*

Fever, widespread skin lesions, and internal organ involvement appear 2 to 8 weeks after introduction of the offending drug. The first sign is typically high fever, which is present in 80% to 90% of patients.[44,45] The rash is usually pruritic and involves more than half of the body surface area. Facial edema occurs in approximately three-quarters of patients.[44] Lesions are usually polymorphous and maculopapular (Fig 4). Less common manifestations are pustules followed by purpura, infiltrated plaques, blisters, targetlike lesions, urticaria, exfoliation, eczema, and, rarely, lichenoid lesions.[44,45] More than half of cases involve the mucosa, usually the oral cavity and lips.[44] Lymphadenopathy is found in approximately 30% to 50% of adult patients and approximately 75% of pediatric patients.[5,44,46]

Almost all cases have hematologic abnormalities. Eosinophilia is present in 50% to 95%,[44-46] but its absence does not exclude the diagnosis; hence, some experts prefer the term drug hypersensitivity syndrome to DRESS syndrome. Most patients have leukocytosis, with atypical lymphocytes in approximately one-fourth to two-thirds of cases.[44,45] Lymphopenia may be present in up to half of cases, and thrombocytopenia has been observed in up to 25% of patients.[45,46]

Liver injury occurs in 75% to 95% of patients.[5,45,46] Nearly 10% of patients may present with liver injury even before skin involvement.[47] Kidney injury occurs in 15% to 40% of patients[5,45,46] and is more prevalent in allopurinol-triggered DRESS syndrome at 60% to 80%.[45,48] Lung involvement occurs in up to one-third of patients[5,46] and is more common in cases related to abacavir, nevirapine, and minocycline.[48] Cardiac involvement is rare overall but relatively frequent in DRESS syndrome triggered by minocycline and nevirapine.[48]

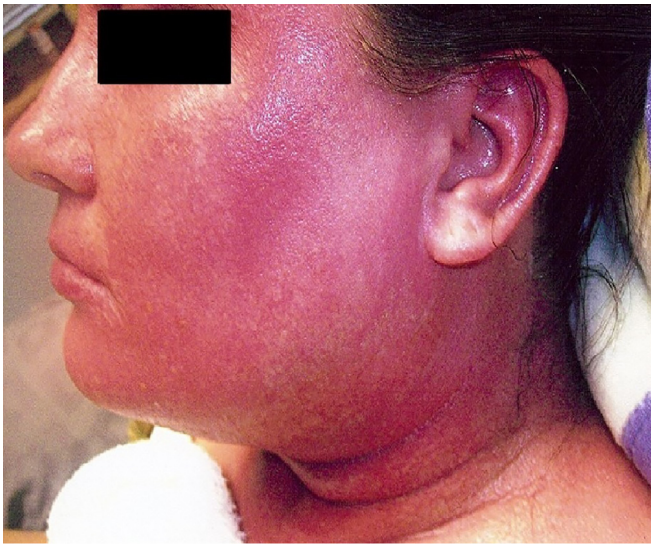

**Figure 4.** Facial edema and diffuse erythema in a young woman with drug reaction with eosinophilia and systemic symptoms syndrome.

The clinical course of DRESS syndrome is prolonged and may include sequential reactivation of various HHVs, particularly HHV-6 and HHV-7, but Epstein-Barr virus and cytomegalovirus infections are seen less frequently.[49-51]

### *Common Offending Agents*

The most frequently associated drugs include carbamazepine, allopurinol, phenytoin, nevirapine, sulfamethoxazole-trimethoprim, sulfasalazine, dapsone, penicillin, nonsteroidal anti-inflammatory drugs, lamotrigine, vancomycin, minocycline, and isoniazid.[44-46] In Han Chinese patients, carbamazepine-induced DRESS syndrome has been linked to HLA-A*31:01 and HLA-B*51:01,[14] and allopurinol-induced DRESS syndrome has been associated with HLA-B*58:01.[51] The time to onset of allopurinol-induced DRESS syndrome is approximately 30 days, longer than with other drugs.[45] Coadministration of omeprazole and phenytoin seems to be a risk factor for DRESS syndrome.[52]

### *Pathogenesis*

DRESS syndrome is a delayed immunologic reaction to a drug in susceptible individuals, including those with a genetic predisposition.[51] Reduced activity of certain metabolizing enzymes may lead to accumulation of the drug or its metabolites, which then elicit an immune response. They may bind to endogenous proteins and then be processed and presented by antigen-presenting cells. Another possibility is that the drugs or metabolites bind to major histocompatibility complex (MHC) proteins or T-cell receptors independently of peptides. Direct binding of the drug or metabolite to the binding groove of MHC proteins could change the peptide specificity of MHC binding. Interleukin (IL) 5, perforin, granzyme B, fatty acid synthase ligand, and IFN-γ have been found in skin biopsy specimens. Viral reactivation may result from drug or metabolite effects directly or from an immunocompromised state in the early stage of DRESS syndrome. Autoimmune sequelae may develop months or years after the resolution of DRESS syndrome because of dysfunction of regulatory T cells.

The histopathologic features of DRESS syndrome are heterogenous and may include nonspecific spongiosis, basal vacuolization, necrotic keratinocytes, dermal-epidermal infiltrates with

lymphocytic exocytosis, dermal edema, and superficial perivascular infiltrates of mostly lymphocytes with or without eosinophils.[25] The presence of apoptotic keratinocytes has been associated with hepatic and renal complications.

### *Management*

The inciting drug must be withdrawn. Establishing causality can be difficult when multiple drugs were taken. Patch testing and delayed intradermal testing can be useful.[53] A recent prospective controlled trial of patients with antibiotic-associated severe cutaneous adverse reactions found that a combination of skin testing (delayed intradermal or patch) and blood testing can be very useful in identifying the culprit. Patients' peripheral blood mononuclear cells were stimulated with a range of implicated antibiotics to measure IFN-γ release from helper and cytotoxic T cells via an enzyme-linked immunoSpot assay.[54] This test had a sensitivity of 52% and specificity of 100%. Combination with skin testing identified the culprit antibiotic in 79% of patients.

Systemic corticosteroids with a gradual tapering during approximately 2 months are the usual treatment, especially for severe cases. A typical starting dose can be oral prednisone, 0.5 mg/kg daily,[49] intravenous methylprednisolone, 40 to 120 mg/d, or oral prednisolone, 30-60 mg/d.[46] In mild cases, potent topical steroids alone, such as betamethasone or clobetasol, may be adequate.[49]

Treatment with IVIG has produced inconsistent results. A recently published series of pediatric patients reported rapid improvement in 24 to 48 hours after administration of IVIG at a dose of 1 to 2 g/kg.[55] However, a prospective study on adult patients treated with IVIG 200 mg/kg daily for 5 days was stopped prematurely because of a high rate of adverse effects.[56] Cyclosporine has been used successfully in 2 cases, with rapid and sustained improvement after a 3- to 7-day course.[57] In a case of steroid-dependent DRESS syndrome, the concomitant administration of anti–IL-5 (mepolizumab, 100 mg every 4 weeks) resulted in disappearance of eosinophilia within a few days and improvement in the rash within 1 week. It allowed the tapering and discontinued use of both drugs by 3 months, without recurrence.[58]

### *Prognosis and Mortality*

DRESS syndrome tends to have a waxing- and waning course, with multiple flares. The skin eruptions typically last 3 to 4 weeks.[50] Approximately 20% of patients still have signs and symptoms 90 days after the disease onset. Internal organs typically recover, but certain patients have required long-term hemodialysis.[46] Mortality is 4% to 10%, mostly from multiorgan failure.[45,46] Acute necrotizing eosinophilic myocarditis has been reported 3 to 4 months after onset of DRESS syndrome, despite apparent improvement in other symptoms.[59]

Long-term autoimmune sequelae include thyroiditis, diabetes type 1, lupus, rheumatoid arthritis, reactive arthritis, alopecia, and vitiligo.[60] Thyroiditis was noted in approximately 5% of survivors in a series from Japan and Taiwan.[60] Autoimmune thyroiditis was also noted within a year after diagnosing DRESS syndrome in European patients, in whom it appeared to be associated with HHV-6 reactivation.[61] Approximately 3% of survivors in the series from Japan and Taiwan developed fulminant type 1 diabetes mellitus within months after resolution of DRESS syndrome.[60] Another Japanese study found a frequency of 0.5% of type 1 diabetes mellitus among DRESS syndrome survivors, which is approximately 50 times higher than in the general Japanese population and associated with HLA-B*62 and HHV-6 reactivation.[62]

## MDH Syndrome

MDH is a syndrome of long-lasting reactions to 2 or more structurally unrelated drugs. It often has different manifestations over the course of weeks, months, or even years.[63]

### *Clinical Presentation*

Most patients with MDH syndrome have had a severe reaction to at least one drug.[64] The initial manifestation can be in the form of DRESS syndrome, although clinical studies suggest that half of patients may have severe exanthema with eosinophilia and elevated liver enzyme levels but without DRESS criteria.[65,66] SJS/TEN is unlikely to be a first reaction.[67]

After administration of unrelated drugs, the patient reacts with symptoms that differ from the first presentation. The manifestations may change to exanthema, erythroderma, AGEP, isolated drug-induced liver dysfunction, exanthema with arthralgia, or any other organ involvement (such as nephritis or pancreatitis).[63,67,68] Agranulocytosis has also been reported.[69] MDH syndrome should be distinguished from flare-up reactions in which patients develop rapid reappearance of similar symptoms after another drug is given. Flare-up reactions occur within a few hours after taking the new drug, and viral reactivation contributes to the clinical presentation.[63,64]

### *Common Offending Agents*

The culprit drugs are chemically unrelated and have no evidence of cross-reactivity.[70] Gex-Collet et al[65] proposed 2 subtypes of MDH syndrome: simultaneous, which develops against different drugs given at the same time, and sequential, in which the sensitizations develop during a long time, sometimes years, apart. Antibiotics are the most commonly involved agents, followed by antiepileptics and antituberculous drugs.[68,70-72] Simultaneous reactivity to 2 drugs in combination therapy is common, for example, sulfamethoxazole and trimethoprim, piperacillin and tazobactam, or amoxicillin and clavulanic acid.[63] Risk factors for the development of MDH syndrome are high drug concentration and long duration of exposure (usually >10-20 days).[63]

### *Pathogenesis*

MDH reactions are mostly T-cell mediated. Massive T-cell stimulation with circulating lymphoblasts typically lasts for weeks to months after the acute reaction. However, drug reactive T cells in a preactivated state can last for longer durations, which may lead to a lower threshold to react to different drugs.[70] No functional deficiency of T-regulatory cells or specific association between MDH and HLA have been noted.[63]

### *Management*

Systemic steroids to suppress the immune reactivity are the primary treatment of MDH syndrome during the reactions.[64] The administration of further drugs should be minimized, and when the addition of a drug is necessary, the lowest effective dose should be given. A drug-free period of days to weeks may also be beneficial.[63] Concomitant administration of a moderate dose of corticosteroids for a few days may reduce the risk of introducing new drugs.[64]

### *Prognosis and Mortality*

The prognosis of patients with MDH syndrome depends on the clinical presentation. Approximately 15% of patients with DRESS syndrome may relapse after the introduction of structurally unrelated drugs.[67] To the best of our knowledge, no information on fatalities attributable to MDH has been reported.

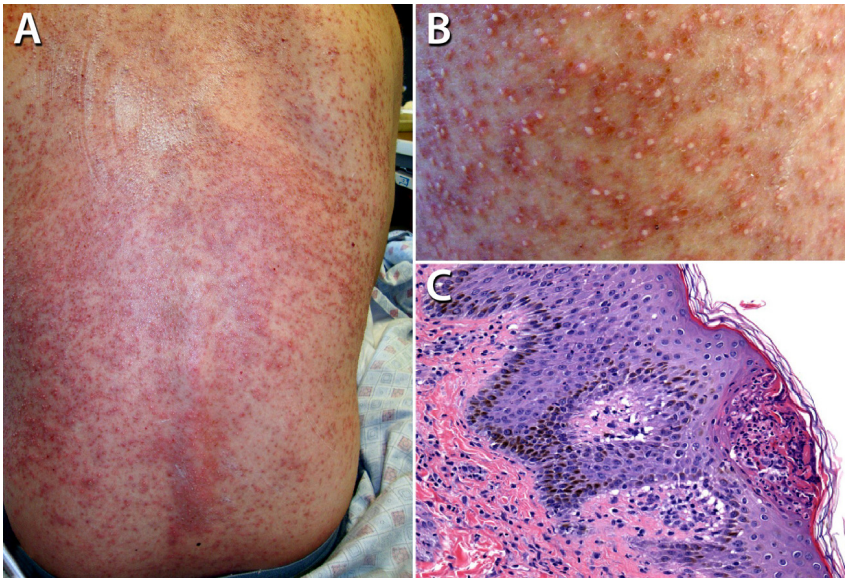


**Figure 5.** Acute generalized exanthematous pustulosis with magnification of the pinhead-sized pustules and the biopsy specimen showing a subcorneal pustule of neutrophils and eosinophils.

## AGEP

AGEP is a severe rash characterized by the rapid formation of sterile pustules. Most cases are attributed to drugs.[73]

### *Clinical Presentation*

Symptoms typically appear within 48 hours of drug exposure. Antibiotic-triggered reactions have a median latency of 24 hours.[74] Patients with AGEP have a rapid onset of dozens to hundreds pinhead-size pustules on a base of erythematous and edematous skin (Fig 5). Lesions usually start in the intertriginous areas or on the face, often with burning or itching sensation.[75] Within a few hours, the rash spreads to the trunk and extremities. Mucosal involvement occurs in approximately one-quarter of patients and is usually limited to a single site. An atypical form of AGEP in which lesions are localized to one specific area is called acute localized exanthematous pustulosis.[76]

In the acute phase, patients exhibit signs of systemic inflammation, such as fever, leukocytosis, neutrophilia, and elevated C-reactive protein level. Eosinophilia is present in approximately 30% of patients.[77,78] Approximately 85% of patients have neutrophilia with some correlation with systemic involvement.[77,78] Multiorgan involvement is present in approximately 20% of patients and includes lymphadenopathy, hepatic dysfunction, nephritis, respiratory failure, or neutropenia attributable to bone marrow involvement.[73,77]

Early diagnosis can be facilitated by dermoscopy, which is skin examination with a magnifier and polarized light. This auxiliary tool may demonstrate the presence of minute pustules in an early stage that grossly appear as diffuse erythema.[79] Biopsy reveals intracorneal, subcorneal, and/or intraepidermal pustules and a dermal infiltrate, mainly consisting of neutrophils and eosinophils (Fig 5). Epidermal changes also include spongiosis with exocytosis of neutrophils and necrotic keratinocytes.[74,79]

### *Common Offending Agents*

Frequently cited causative drugs are aminopenicillins, pristinamycin, sulfonamides, quinolones, hydroxychloroquine, terbinafine, and diltiazem.[80] AGEP may also be associated with infections such as parvovirus B19, cytomegalovirus, coxsackie B4, *Mycoplasma pneumoniae*, and Epstein-Barr virus.[80,81]

### *Pathogenesis*

AGEP is a T-cell–related neutrophilic inflammatory response in which drug-specific cytotoxic T cells use granzyme B and perforin to induce apoptosis of keratinocytes within the epidermis, leading to tissue destruction and vesicle formation.[73] During initial stages, the vesicles are composed of $CD4^+$ T cells and keratinocytes. These cells release CXCL8/IL-8 for neutrophil recruitment into the vesicles.[74]

### *Management*

In addition to discontinuation of use of the suspected causative agent(s), topical corticosteroids and disinfectant solutions can be used during the pustular phase.[82] Rehydrating lotions are useful during the desquamative phase.[73] Systemic steroids may be used in severe cases, but there is no evidence that they reduce the disease duration.[75,83] If the suspected medications are multiple, patch testing after resolution often identifies the culprit drug by eliciting small localized pustules.[73]

### *Prognosis and Mortality*

Skin lesions usually spontaneously resolve within 2 weeks. However, some patients with severe disease may require management in an intensive care unit.[77] The pustules progress to characteristic desquamation with a narrow rim of loosened keratin overhanging the periphery of the lesion (described as collarette shaped). Superinfection of the skin can be life-threatening in patients with poor general condition,[75] and the overall estimated mortality is less than 5%.[73]

## DIBP

Bullous pemphigoid is primarily an autoimmune disorder that affects elderly individuals and causes subepidermal blistering.[84] The drug-induced variant follows oral or topical administration of a drug and can be difficult to differentiate clinically from the classic autoimmune form.[85]

### *Clinical Presentation*

Pruritic lesions may appear several months after initiating use of the offending drug.[85] Tense bullae are located on the face, trunk, and

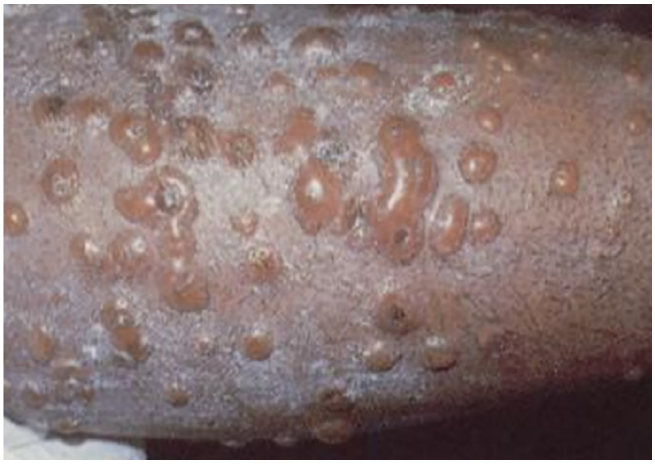

**Figure 6.** Tense bullae characteristic of bullous pemphigoid.

limbs, particularly the lower legs (Fig 6). The surrounding skin typically appears normal but can display erythema or urticaria in rare cases. Target lesions may appear on the palms and soles. DIBP generally presents in younger patients than those affected by the spontaneous autoimmune form. Mucosal involvement is mild and not always present. Eosinophilia is often present.[86]

*Common Offending Agents*

In many reported cases, the patients were receiving multiple drugs, making identification of the culprit difficult. Literature from recent years has identified several new groups of medications associated with the appearance of DIBP.[85-89] Frequently cited triggers are angiotensin-converting enzyme inhibitors, diuretics, antibiotics, nonsteroidal anti-inflammatory drugs, neuroleptics, antidiabetics, and antiarrhythmics. Vaccines and topical agents have also been implicated. Some cases were even caused by TNF-α inhibitors that have been used to treat bullous pemphigoid.[85]

*Pathogenesis*

Theories on the pathogenesis of DIBP include inactivation of endogenous regulatory processes, molecular mimicry (drugs are mistaken for microbial antigens), and the possibility that drugs directly interact with the basement membrane and change its antigenic properties.[85] The typical histologic finding is subepidermal blisters with eosinophils, intraepidermal vesicles, and necrotic keratinocytes.[84] Direct immunofluorescence demonstrates the characteristic linear deposition of IgG and C3 along the basement membrane, similar to classic bullous pemphigoid.[85]

*Management*

In addition to discontinuation of use of the suspected offending agent(s), systemic corticosteroid therapy can enhance recovery. Mild cases may respond to a high-potency topical corticosteroid, such as clobetasol propionate. Oral prednisolone at 0.5 mg/kg daily is typically used for moderate to severe disease.[90] Oral steroids should be tapered gradually based on the clinical course of the disease.[85] Immunosuppression with mycophenolate mofetil (2-3 g/d), azathioprine (1.5-2.5 mg/kg daily), or, less commonly, methotrexate (10-50 mg/wk) is indicated in resistant cases.[90,91]

*Prognosis and Mortality*

Most cases of DIBP achieve complete remission within 6 weeks of starting treatment and, unlike the autoimmune variety, rarely relapse.[85] Fatalities are rare but secondary infection of the skin prolongs the course to recovery.

## Conclusion

Certain rashes reflect serious drug reactions such as SJS, TEN, DRESS, MDH syndrome, AGEP, and DIBP. They should be recognized early (Table 2). Prompt management includes immediate discontinuation of the suspected drug(s) and personalized symptomatic therapy. With the lack of reliable tests, identification of the culprit drug can be difficult in patients receiving multiple medications. To

**Table 2**
Characteristics of Selected High-Risk Drug Rashes

| Disease | Morphologic findings | Latency | Symptoms | Systemic involvement | Laboratory findings | Histology | Duration |
|---|---|---|---|---|---|---|---|
| SJS<br>TEN | Epidermal necrosis <10% BSA<br>Epidermal necrosis >30% BSA | 1-3 wk | Malaise, skin pain, headache, eye pain, pharyngitis, myalgia | Infections (ie, pneumonia, bacteremia), respiratory failure, shock | Possibly leukocytosis, increased CRP concentration and ESR | Full-thickness keratinocyte necrosis and subepidermal bullae | 2-3 wk |
| DRESS | Polymorphous, maculopapular rash on >50% BSA | 2-8 wk | Fever, lymphadenopathy, pruritus | Liver and kidney injury | Eosinophilia in 50%-95%, atypical lymphocytes | Heterogenous nonspecific, lymphocytic infiltrate | 3-4 wk with waxing and waning |
| MDH | Each reaction is variable but often similar to DRESS | >3 d to years after initial reaction | Variable depending on manifestation of reaction | Liver failure, nephritis, pancreatitis | Elevated liver enzyme concentrations, eosinophilia, lymphocytosis, agranulocytosis | Variable, depending on manifestation of reaction | Variable |
| AGEP | Pinhead-sized pustules on erythematous, edematous base | Within 48 h | Burning sensation or pruritus | Lymphadenopathy, liver injury, kidney injury, respiratory failure, neutropenia | Leukocytosis, neutrophilia, eosinophilia, increased CRP concentration | Intracorneal, subcorneal and/or intraepidermal pustules | <2 wk |
| DIBP | Tense bullae on skin appearing normal or inflamed, target lesions on palms and soles | Up to 3 mo | Intense pruritus | Uncommon | Eosinophilia | Subepidermal blisters, intraepidermal vesicles, necrotic keratinocytes; linear IgG and C3 along basement membrane | <6 wk |

Abbreviations: AGEP, acute generalized exanthematous pustulosis; BSA, body surface area; CRP, C-reactive protein; DIBP, drug-induced bullous pemphigoid; DRESS, drug reaction with eosinophilia and systemic symptoms; ESR, erythrocyte sedimentation rate; MDH, multiple drug hypersensitivity syndrome; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis

minimize the risks of morbidity and mortality, close monitoring of the vital organs function is of great importance and management requires team collaboration by various medical specialists.

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