

Stevens-Johnson syndrome and toxic epidermal necrolysis: Pathogenesis, clinical manifestations, and diagnosis

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INTRODUCTION AND CLASSIFICATION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions characterized by extensive necrosis and detachment of the epidermis. Mucous membranes are affected in more than 90 percent of patients, usually at two or more distinct sites [1].

SJS and TEN exist as a continuum and are classified based on the percentage of skin body surface area (BSA) detached [2]:

- <10 percent of BSA detached – SJS
- 10 to 30 percent of BSA detached – SJS/TEN overlap
- >30 percent of BSA detached – TEN

The term "epidermal necrolysis" has been used to refer collectively to SJS, SJS/TEN overlap, and TEN [3].

The pathogenesis, clinical manifestations, and diagnosis of SJS/TEN are discussed in this topic. Treatment, prognosis, and long-term complications are discussed separately. Other drug eruptions are reviewed elsewhere.

- (See "Stevens-Johnson syndrome and toxic epidermal necrolysis: Management, prognosis, and long-term sequelae".)
 - (See "Drug reaction with eosinophilia and systemic symptoms (DRESS)".)
 - (See "Acute generalized exanthematous pustulosis (AGEP)".)
 - (See "Exanthematous (maculopapular) drug eruption".)
 - (See "Fixed drug eruption".)
 - (See "Lichenoid drug eruption (drug-induced lichen planus)".)
 - (See "Acneiform eruption secondary to epidermal growth factor receptor (EGFR) and MEK inhibitors".)
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EPIDEMIOLOGY

Incidence — SJS/TEN is a rare condition. The estimated incidence across the disease spectrum is five to six cases per million per year [4-6]. In the United States, the incidence of SJS, SJS/TEN, and TEN in the pediatric population was 5.3, 0.8, and 0.4 cases per million children per year, respectively [7].

In a multinational case-control study that included 379 cases, the median age was 50 years [8]. Similarly, in another French study of 2635 incident cases from four national databases, the median age was 52 years [5].

SJS/TEN is more common in females, with a female-to-male ratio of approximately 2:1 [9].

Risk factors

- **Human immunodeficiency virus** – Patients with human immunodeficiency virus (HIV) infection have an increased risk of SJS/TEN. In European cohort studies, the prevalence of HIV infection among patients with SJS/TEN was 7 to 9 percent; patients with HIV infection had a 12-fold increased risk of SJS/TEN [9,10]. In a retrospective study of 177 cases of SJS/TEN treated in dermatology departments/intensive care units in sub-Saharan Africa, the prevalence of HIV infection was 55 percent [11]. This heightened risk for SJS/TEN in patients with HIV infection is likely due to multiple factors, including the use of high-risk medications for the treatment of HIV (eg, [nevirapine](#)) and opportunistic infections (eg, co-trimoxazole, tuberculosis medications) as well as the immune dysregulation associated with HIV [12-14].

- **Connective tissue disease** – Patients with connective tissue disease have a twofold increased risk of SJS/TEN compared with patients without connective tissue disease [8,15]. However, because acute forms of cutaneous lupus erythematosus may mimic TEN (TEN-like lupus erythematosus), the risk may be overestimated.
- **Malignancy** – Patients with cancer have an increased risk of SJS/TEN. In a case-control study (EuroSCAR) of 379 cases and 1505 controls, a recent cancer diagnosis and radiation therapy were more common among cases of SJS/TEN, occurring in 10.6 and 4.2 percent versus 1.9 and 0.5 percent in controls, respectively [8]. In an analysis of a large cohort of over 100,000 patients with cancer identified from electronic health records between 2002 and 2015, the estimated annual incidence of confirmed and possible cases of SJS/TEN were 5.7 and 14.9 per 100,000 per year, respectively [16]. These rates are approximately 30 to 60 times higher than in the general population. In that cohort, the most common triggers were [trimethoprim-sulfamethoxazole](#), [phenytoin](#), and idiopathic causes.
- **Older adults** – The incidence of SJS/TEN is higher in older patients. In an analysis of four French databases, the estimated annual incidence of SJS/TEN among individuals ≥65 years was 13.7 cases per million compared with 4.1 cases per million among individuals <20 years of age and 3.9 cases per million among those aged 20 to 64 years [5].
- **Ethnicity** – A United Kingdom study utilizing the Clinical Practice Research Datalink from 1995 to 2013 found a twofold and threefold increased risk of SJS/TEN among Black and Asian people, respectively, compared with White people [6]. Similar findings were reported in a study from the United States using data from the Nationwide Inpatient Sample from 2009 to 2012 [4].
- **Other factors** – Increased drug doses and impaired renal function have been associated with an increased risk of allopurinol-induced SJS/TEN [17-19].

Mortality — In a comprehensive survival analysis of a cohort of patients recruited from Austria, France, Germany, Israel, Italy, and the Netherlands (Registry of Severe Cutaneous Adverse Reactions [RegiSCAR]; n = 460), the overall mortality rate for SJS/TEN during the acute episode was 23 percent, varying from 12 to 49 percent across the SJS/TEN severity spectrum [9]. However, at one year, the overall mortality for SJS/TEN increased to 34 percent, likely due to severe comorbidities and older age.

Based on data from the 2009 to 2012 Nationwide Inpatient Sample, the mortality in the pediatric population was 0 percent for SJS, 4 percent for SJS/TEN, and 16 percent for TEN [7].

ETIOLOGY

Medications — In most cases, SJS/TEN is a severe cutaneous reaction to medications.

- **High-risk medications** – Although the list of causative medications is long, several epidemiologic studies have demonstrated that the majority of such cases are due to a group of high-risk medications ([table 1](#)) [8,20-22].

Several novel anticancer therapies, such as immune checkpoint inhibitors (ICIs; eg, [ipilimumab](#), [pembrolizumab](#), [nivolumab](#), [atezolizumab](#)), have been associated with SJS/TEN [23,24]. Based on a meta-analysis of 20 randomized trials (11,597 patients), the use of ICIs was associated with a fourfold increased risk of SJS/TEN [25]. These reactions occurred at a median of 26 days since starting treatment, and the overall mortality was 37 percent [26].

However, some ICI-related cases may represent SJS/TEN-like reactions that mimic SJS/TEN clinically and/or histologically [27-29]. Unlike true SJS/TEN, ICI-induced SJS/TEN-like reactions are believed to be severe immune-mediated bullous eruptions due to enhanced ICI cytotoxicity [26,29,30]. (See "[Cutaneous immune-related adverse events associated with immune checkpoint inhibitors](#)".)

- **Timing** – The causative medication is typically started between one week to one month (occasionally up to two months) prior to the onset of symptoms. Drugs that are prescribed outside of this "at-risk" period are unlikely to be the cause of SJS/TEN.
- **Protopathic bias** – Caution must be exercised to avoid the so-called "protopathic bias," whereby medications that are used to treat the initial symptoms of SJS/TEN (eg, flu/cold medications, antibiotics) are erroneously assumed to be the culprits for the reaction.

Other causes — In at least 15 percent of cases, no clear drug causality can be found [22].

- **Infection** – *Mycoplasma* infection has been identified in less than 30 percent of such idiopathic cases and should be considered when drug causality is unclear [31]. However, *Mycoplasma* and other bacterial or viral infections have been associated with a severe reactive mucositis with limited cutaneous involvement that is considered a separate entity. (See "[Reactive infectious mucocutaneous eruption \(RIME\)](#)".)
- **Other causes** – There are rare and controversial reports of SJS/TEN attributed to chemical exposure [32], complementary/traditional medications [33], vaccinations [34-37], and foods [38].

- **Idiopathic SJS/TEN** – In at least 15 percent of cases, no clear exposure to drugs or other triggers can be identified [22]. Whether occult exposures to drugs present in complementary medications, foods, or yet-to-be-identified infectious agents are implicated in idiopathic cases has not been determined [39,40].
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PATHOGENESIS

SJS/TEN is predominantly a drug-specific T cell-mediated reaction. The human leukocyte antigen (HLA)-drug-T cell receptor (TCR) engagement results in the activation of drug-specific CD8+ T cells with subsequent release of cytotoxic proteins, resulting in epidermal necrolysis [41-44].

The main pathogenic sequence can be summarized as follows:

- Genetic predisposition (HLA polymorphism and pharmacogenetics)
- Drug antigen presentation
- T cell-mediated response and immune dysregulation
- Release of cytotoxic mediators, death signals, and keratinocyte cell death

HLA polymorphism and pharmacogenetics — A genetic predisposition to SJS/TEN has been established. The association of certain HLA haplotypes with an increased risk of SJS/TEN is restricted to certain ethnicities and specific drugs ([table 2](#)). Examples of at-risk HLA phenotypes include HLA B*5801 in Han Chinese, Malay, Thai, European, and Korean populations in relation to allopurinol-induced SJS/TEN [44-46] and HLA B*1502 in Han Chinese, Thai, and Malay populations in relation to carbamazepine-induced SJS/TEN [44,47,48].

Genome-wide association studies have further identified other genetic variants that may increase the risk of SJS/TEN. These include variants in cytochrome P450 2C9 enzyme, which reduces drug clearance and is associated with phenytoin-related severe cutaneous adverse reactions [49], as well as a slow acetylator genotype that increases the risk for sulfonamide-induced TEN [50,51]. Additionally, adenosine triphosphate (ATP)-binding cassette (ABC) transporters and proteosome complex have been implicated [52].

Screening for HLA B*1502 is recommended in patients of Asian ancestry prior to initiating treatment with [carbamazepine](#) [53]. Several studies have shown the reduction of SJS/TEN with the use of preinitiation genetic screening in Asian countries such as Taiwan, Singapore, and Thailand [54,55]. (See "[Seizures and epilepsy in children: Initial treatment and monitoring](#)", section on '[Role of pretreatment HLA testing](#)').

Models of drug-induced T cell activation — HLA-drug-TCR synapse is the initial step in the pathogenesis of SJS/TEN. Various models have been proposed to explain how the inciting drug is recognized by TCRs to activate adaptive responses:

- **Hapten/prohapten model** – The drug/metabolite binds covalently to an endogenous protein that undergoes intracellular processing. When these modified peptides are presented with an HLA molecule to the TCRs on T cells, they are recognized as foreign, and an immune response is elicited. The model has been used to explain beta-lactam-induced drug hypersensitivity [56].
- **Pharmacologic interaction of drugs with immune receptors model** – The drug/metabolite binds directly and noncovalently to the HLA molecule or TCR. This has been demonstrated for HLA B*1502 and carbamazepine-associated SJS/TEN [57,58].
- **Altered peptide model** – In this model, the binding of the drug to HLA results in a conformational change, thereby altering the HLA binding specificity. This allows for a new repertoire of self-peptides to be bound and presented, resulting in an alloreactive T cell response. This model has been used to demonstrate [abacavir](#) drug hypersensitivity [59,60].
- **Altered T cell receptor model** – Similar to the altered peptide model, binding of the drug/metabolite to TCR results in a conformational change, altering the specificity of HLA self-peptides [61].

T cell-mediated response and immune dysregulation — The main cellular effectors of SJS/TEN are CD8+ cytotoxic T cells, which possess the relevant TCR clonotypes to facilitate the HLA-drug-TCR engagement [42,62,63]. This interaction results in the activation of the cytotoxic CD8+ T cells with the subsequent release of cytotoxic proteins, resulting in epidermal necrolysis. Besides cytotoxic T cells, other involved cellular mediators include natural killer (NK)/T cells, NK cells, and T helper type 17 (Th17) cells as evidenced by their presence in TEN blister fluids [64]. In addition, the impairment of T regulatory cell function during the acute phase may potentiate the immune dysregulation [65].

Cytotoxic mediators, death signals, and cell death — Fulminant keratinocyte death and full-thickness epidermal detachment marks the final stage of TEN pathogenesis. Various cytotoxic proteins and cytokines, such as soluble granulysin, Fas ligand, perforin/granzyme, tumor necrosis factor (TNF)-alpha, and TNF-related apoptosis-inducing ligand, have been proposed as mediators [64,66-68]. Granulysin, a cytolytic protein found in cytotoxic T cells, NK/T cells, and NK cells, is now recognized as the most important mediator of keratinocyte death in SJS/TEN [64].

The predominant mechanism of cell death in TEN is thought to be apoptosis [69]. However, studies suggest that necroptosis, a form of programmed cell death with necrosis and inflammation, may play a role as well. Necroptosis may be mediated via annexin A1/RIP3 pathways [70-72].

Various cytokines/chemokines have also been implicated in SJS/TEN. TNF-alpha is increased [73], and interleukin (IL) 15 is associated with mortality and severity [74]. IL-15 is a widely expressed cytokine produced by many cell types, including immune cells (eg, monocytes, macrophages, and dendritic cells) and keratinocytes. IL-15 has a key role in promoting and maintaining long-lasting cytotoxic T cell and NK cell responses. In in vitro models, the addition of exogenous IL-15 has been shown to increase the secretion of granulysin and, to a lesser extent, of granzyme from blister fluid cells from patients with TEN [74].

In addition to these mediators, other cytokines such as interferon (IFN)-gamma, IL-2, IL-5, IL-6, IL-10, IL-12, IL-13, IL-18, IL-33, CCR3, CXCR3, CXCR45, and CCR10 may be involved in the trafficking, proliferation, and activation of T cells as well as the amplification of both the innate and acquired immune response [25,75-77].

Apart from the adaptive immune system, the innate system has been increasingly implicated in the disease mechanism. Neutrophils have been implicated in the activation and amplification of TEN via neutrophil extracellular traps [78]. Induction and increased expressions of alarmins have also been observed in TEN [77,79].

CLINICAL PRESENTATION

Prodromal symptoms — Prodromal symptoms of SJS/TEN include malaise, fever, myalgia, sore throat, and conjunctivitis. These symptoms may precede or occur concurrently with the mucocutaneous presentation [1,80,81].

Cutaneous lesions — The initial cutaneous presentation of SJS/TEN may mimic an exanthematous rash. Lesions start on the face and thorax before spreading to other areas and are symmetrically distributed. Early lesions typically begin with ill-defined, coalescing, erythematous macules, which evolve over the course of one to two days to develop dusky erythema, purpuric spots, atypical targets (atypical targets have two rings instead of the three typically seen in target lesions of erythema multiforme), and flaccid bullae (picture 1A-C).

As the disease progresses, extensive, sheet-like detachment and erosions occur (picture 2A-B). Nikolsky sign (the ability to extend the area of epidermal detachment with

gentle lateral pressure) is positive. The scalp is typically not affected; painful, edematous erythema typically develops on the palms and soles ([picture 3](#)) [1,80,81].

Skin tenderness is prominent in SJS/TEN, and the diagnosis must be suspected in anyone who presents with a tender, extensive, mucocutaneous eruption.

The acute, progressive phase of the disease lasts for approximately seven to nine days from initial symptoms before the process arrest. From disease arrest, the skin re-epithelializes over 7 to 21 days [3,82].

During the active phase of the disease, the patient is at risk of fluid and electrolyte imbalances, increased metabolic demands, sepsis, hypothermia, organ decompensation, and death due to the extensive skin detachment ("skin failure") [1,81,83].

Extracutaneous involvement and complications

Mucosal involvement — All mucosal surfaces can be involved during the acute phase of the disease and often include the buccal, oro/nasopharyngeal, and anogenital mucosa. In up to 80 percent of patients, two or more mucosal surfaces are involved [1,80]. Oral cavity involvement is the most common (90 percent of patients), followed by nasal (50 percent), ear (50 percent), and laryngeal involvement (30 percent) [84].

- Oral mucosal involvement may take the form of erosions, blisters, and hemorrhagic cheilitis ([picture 4A-B](#)). Nasopharyngeal involvement may include erosions, blisters, epistaxis, and epiglottitis. Severe laryngeal involvement may be associated with a higher risk of acute pulmonary involvement.
- Genital involvement can be seen in up to 60 to 70 percent of patients and commonly presents as erosions and blisters [85,86]. Extensive pain and dysuria may lead to acute urinary retention. In females, vulvovaginal involvement may present with erosive and ulcerative vaginitis, vulvar bullae, vaginal synechiae, and may lead to long-term anatomic sequelae. These include labial and vaginal adhesions and stenosis [87,88].

Eye involvement — Ocular involvement is common (affecting 60 to 100 percent of patients) and may present as conjunctival hyperemia ([picture 5](#)), pseudomembrane formation, or complete corneal epithelial defect [89]. Acute ocular surface involvement can be graded as follows [90]:

- No ocular involvement – 0 (none)
- Conjunctival hyperemia – 1 (mild)
- Either ocular surface epithelial defect or pseudomembrane formation – 2 (severe)

- Both ocular surface epithelial defect and pseudomembrane formation – 3 (very severe)

Acute ocular involvement is the strongest predictor for long-term ocular complications [91-93]. Between 20 to 75 percent of SJS/TEN survivors have chronic eye sequelae, which include lid ectropion/entropion; trichiasis; distichiasis; symblepharon and forniceal shortening; persistent corneal epithelial defect, thinning, scarring, and keratinization; dry eyes; and reduced visual acuity [91,94,95]. (See "[Stevens-Johnson syndrome and toxic epidermal necrolysis: Management, prognosis, and long-term sequelae](#)", section on 'Eyes'.)

Renal involvement — Acute kidney injury is common and has been reported in approximately 20 to 30 percent of SJS/TEN cases [96,97]. Proteinuria can occur in up to 60 percent of patients [98]. In a French retrospective cohort study that included 245 patients admitted for SJS/TEN, renal replacement therapy was initiated in approximately 10 percent of patients during their hospital stay [99]. Risk factors for renal replacement therapy include the presence and severity of acute renal failure on admission, larger body surface area (BSA) involvement, and score of toxic epidermal necrolysis (SCORTEN) values. Patients requiring renal replacement therapy had a significantly higher in-hospital mortality than those not requiring it (82 versus 9 percent) [99].

Pulmonary involvement — During the acute phase of the disease, respiratory complications are frequent. These include specific lung injury (eg, sloughing of the bronchial epithelium), as well as nonspecific complications, such as pneumonia, pulmonary edema, and atelectasis. Twenty-five percent of patients with pulmonary involvement may develop acute respiratory failure requiring mechanical ventilation [100].

Gastrointestinal involvement — Gastrointestinal involvement in SJS/TEN is not well defined. Clinical presentations may include abdominal pain, diarrhea, hematemesis, melena/rectal bleeding, or ileus. In a retrospective review of 20 patients with SJS/TEN admitted to an intensive care unit who underwent endoscopic procedures, 11 patients (55 percent) had definite SJS/TEN-related lesions (eg, epithelial detachment, mucosal ulceration, stricture) mostly involving the esophagus [101].

Liver injury — In a study of 298 cases of SJS/TEN from China, drug-induced liver injury occurred in 40 patients (13 percent) [102]. In another cohort from Australia, drug-induced liver injury occurred in up to 30 percent of patients with SJS/TEN. Independent risk factors for drug-induced liver injury include underlying liver disease, hyperlipidemia, and diabetes [103].

Hematologic abnormalities — Hematologic abnormalities (eg, anemia, leukopenia, thrombocytopenia) are common in SJS/TEN [80]. In a review of 377 patients with SJS/TEN, 13 percent of patients had leukopenia during the acute phase of the disease [104]. Disseminated

intravascular coagulation has been reported in over 20 percent of patients with SJS/TEN [105,106].

Bacteremia and sepsis — Bacteremia occurs in up to 30 to 50 percent of patients with SJS/TEN and is associated with a three- to fourfold increased mortality risk. Sepsis and septic shock are the main causes of death in these patients, accounting for approximately 50 percent of deaths from SJS/TEN.

Risk factors for bacteremia include age >40 years, white blood cell >10,000, BSA involvement >10 percent, hemoglobin <10 g/dL, and underlying cardiovascular diseases [107-109]. Bacteremia is most often caused by *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and other gram-negative bacteria. In specialized burn units and intensive care units, nosocomial organisms (eg, *Acinetobacter baumannii*) may also be isolated [108,109].

DIAGNOSIS

The diagnosis of SJS/TEN is based on clinical presentation, history, and supportive histologic evidence.

Clinical findings and history — The diagnosis of a severe cutaneous adverse reaction should be suspected in any patient presenting with a sudden onset of a painful mucocutaneous eruption associated with systemic symptoms and a history of recent exposure to drugs (table 1).

Drug causality assessment — Drug causality assessment hinges on two factors:

- **Latency** – An exposure to the suspected drug for an extended period of one to four weeks (less commonly eight weeks) prior to the onset of the reaction.
- **Drug notoriety** – Information about the drugs that are most frequently associated with SJS/TEN, based on epidemiologic studies and pharmacovigilance, is helpful for the diagnosis (table 1).

The algorithm of drug causality for epidermal necrolysis (ALDEN) has been developed as a tool for the rapid assessment of drug causality (table 3). ALDEN is based on six parameters, including drug notoriety, half-life, latency, rechallenge results, and presence of alternative explanations [22]. The ALDEN score is especially useful for clinicians who may be unfamiliar with the assessment of drug causality in severe cutaneous reactions.

Skin biopsy — A skin biopsy for routine histopathologic examination and direct immunofluorescence may be helpful for supporting the diagnosis of SJS/TEN and excluding other disorders that may mimic SJS/TEN. (See '[Differential diagnosis](#)' below.)

Classic histopathologic features of SJS/TEN include basal keratinocyte apoptosis in the early stage of the disease, evolving to full-thickness necrolysis and separation of the epidermis at the dermo-epidermal junction as the disease progresses. The dermal inflammatory infiltrate is typically mild and consists primarily of T lymphocytes [110]. Direct immunofluorescence is always negative [111].

Laboratory and imaging studies — The laboratory and imaging evaluation of patients with SJS/TEN includes:

- Complete blood count with differential, coagulation studies, metabolic panel (ie, glucose, electrolytes, blood urea nitrogen, creatinine, calcium, total protein, albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase), erythrocyte sedimentation rate, and C-reactive protein.
- Bacterial and fungal cultures should be performed from blood, wounds, and mucosal lesions. Because of the high risk of bacterial superinfection and sepsis, cultures should be repeated at frequent intervals during the acute phase of the disease.

Procalcitonin may be useful as an early diagnostic marker of bacteremia. The presence of raised procalcitonin and hypothermia has been associated with a higher incidence of blood culture positivity [107]. Skin cultures have good negative predictive values for *S. aureus* and *P. aeruginosa* bacteremia if skin swabs are negative for these organisms [109]. (See "[Sepsis syndromes in adults: Epidemiology, definitions, clinical presentation, diagnosis, and prognosis](#)".)

- In children, as well as in adults without a clear drug causality, polymerase chain reaction and/or serology for *Mycoplasma pneumoniae* infection should be obtained in the early stage of disease and three weeks later. (See "[Mycoplasma pneumoniae infection in children](#)", section on '[Diagnosis](#)').
- A chest radiograph should be obtained in all patients due to the possibility of pulmonary involvement of SJS/TEN, pneumonia, and interstitial pneumonitis (see '[Pulmonary involvement](#)' above). If indicated, other imaging modalities/procedures, such as computed tomography (CT) scans and bronchoscopy, may be necessary.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of SJS/TEN includes:

- **Erythema multiforme** – Erythema multiforme (EM) is an immune-mediated disorder most commonly triggered by infections and characterized by an eruption of typical target lesions ([picture 6A-C](#)), which are circular papules and plaques with three distinct rings (a darker center with or without a blister followed by a pale, pink ring and a bright red, outermost ring). Distribution of EM is typically acral, and the extent of involvement is usually limited. In contrast, target lesions in SJS/TEN are atypical (flat and lacking the three rings) and distributed on the trunk and head/neck. Moreover, dusky erythema, flaccid bulla, and sheet-like skin detachment do not occur in EM. On histology, EM demonstrates an interface dermatitis with a lichenoid infiltrate and epidermal necrosis that is mainly limited to the basal layer, whereas in SJS/TEN, there is extensive epidermal necrosis with minimal inflammatory infiltrate [111]. (See "[Erythema multiforme: Pathogenesis, clinical features, and diagnosis](#)".)
- **Exanthematous drug eruptions** – The generalized and symmetric maculopapular erythema of an exanthematous drug eruption can mimic the initial presentation of SJS/TEN ([picture 7A-B](#)). However, exanthematous drug eruptions lack mucosal involvement, the prominent skin pain of TEN, blisters, and epidermal detachment [112]. Histology may show only a mild interface dermatitis with a perivascular, inflammatory infiltrate of lymphocytes, neutrophils, and eosinophils without the full-thickness epidermal necrolysis ([picture 8](#)). (See "[Exanthematous \(maculopapular\) drug eruption](#)".)
- **Drug reaction with eosinophilia and systemic symptoms** – The cutaneous eruption of drug reaction with eosinophilia and systemic symptoms (DRESS) is widespread and may be polymorphous, ranging from an exanthematous eruption to confluent erythema to generalized exfoliative dermatitis. Sheet-like detachment is never present ([table 4](#)). Facial edema is prominent. Mucosal involvement is infrequent and typically mild. Ocular involvement is rare. In addition to the cutaneous findings, systemic involvement and lymphadenopathy are frequently present [113]. (See "[Drug reaction with eosinophilia and systemic symptoms \(DRESS\)](#)".)
- **Acute generalized exanthematous pustulosis** – Severe cases of acute generalized exanthematous pustulosis (AGEP) may be difficult to differentiate from SJS/TEN ([table 4](#)) [114]. AGEP typically develops within a few days of exposure to the offending drug, most often a beta-lactam antibiotic. Clinical features include numerous pinpoint pustulosis on a

background of erythema ([picture 9](#)). The condition resolves without treatment in one to two weeks after drug discontinuation. The histologic hallmark of AGEP is a spongiform, subcorneal, and/or intraepidermal pustule ([picture 9](#)). (See "[Acute generalized exanthematous pustulosis \(AGEP\)](#)".)

- **Generalized bullous fixed drug eruption** – Generalized bullous fixed drug eruption is characterized by discrete, well-defined, large, dusky, violaceous patches with or without blisters or erosions. The intervening areas between lesions are typically spared. Although the mucosae can be involved, ocular involvement is never present [115]. (See "[Fixed drug eruption](#)", section on '[Generalized bullous fixed drug eruption](#)').
- **Staphylococcal scalded skin syndrome** – Staphylococcal scalded skin syndrome (SSSS) is a disorder primarily affecting young children although it may occur in adults in the setting of immunosuppression, chronic kidney disease, and other severe comorbidities. SSSS is characterized by painful erythema, extensive peeling, and erosions. Mucous membranes are not affected. Histopathology can differentiate SSSS and SJS/TEN. (See "[Staphylococcal scalded skin syndrome](#)".)
- **Acute graft-versus-host disease** – Acute graft-versus-host disease (GVHD) is a complication of allogenic hematopoietic stem cell transplant. The most severe form of GVHD (grade 4) has similar clinical findings of widespread erythema, blistering, and oral mucositis, although the clinical course is subacute. (See "[Cutaneous manifestations of graft-versus-host disease \(GVHD\)](#)".)
- **Reactive infectious mucocutaneous eruption** – Reactive infectious mucocutaneous eruption (RIME) is a reactive parainfectious mucocutaneous eruption that is commonly attributed to *Mycoplasma* and other infective agents, such as *Chlamydia pneumoniae*, human metapneumovirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, parainfluenza, and influenza B virus. Although mucositis is prominent ([picture 10](#)), often affecting two or more mucous membranes, cutaneous involvement is typically limited or absent [116]. (See "[Reactive infectious mucocutaneous eruption \(RIME\)](#)".)
- **SJS/TEN-like acute cutaneous lupus erythematosus** – This is a rare manifestation of systemic lupus erythematosus that mimics TEN clinically. Differentiation between the two may be challenging. In SJS/TEN-like acute lupus, the skin lesions may be photodistributed; associated with a recent flare of lupus; and have a longer, protracted clinical course. In addition, although the oral mucosa may be involved in SJS/TEN-like lupus, genital and ocular involvement are uncommon. On histology, the finding of junctional vacuolar

alteration associated with a moderate to dense periadnexal and perivascular lymphocytic infiltrate with melanophages and mucin points to a lupus erythematosus-related origin. Direct immunofluorescence is rarely positive in TEN-like lupus erythematosus cases but, if present, suggests an lupus erythematosus diagnosis [15,117]. (See "[Overview of cutaneous lupus erythematosus](#)", section on '[Acute cutaneous lupus erythematosus](#)').

- **Paraneoplastic pemphigus** – Paraneoplastic pemphigus is a rare disorder that can represent the initial presentation of a malignancy or occur in a patient with a known neoplastic process, such as non-Hodgkin lymphoma in adults or Castleman disease in children. Patients may develop severe mucocutaneous disease with ocular and oral blisters and skin lesions ([picture 11A-C](#)). (See "[Paraneoplastic pemphigus](#)".)
- **Linear IgA bullous dermatosis** – Linear IgA (immunoglobulin A) bullous dermatosis is a rare autoimmune blistering disease that may mimic TEN ([picture 12](#)). Histology reveals a subepidermal blister with an underlying, neutrophil-predominant, dermal infiltrate. Direct immunofluorescence shows linear deposits of IgA along the basement membrane. (See "[Linear IgA bullous dermatosis](#)".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "[Society guideline links: Drug allergy and hypersensitivity](#)".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "[Patient education: Stevens-Johnson syndrome and toxic epidermal necrolysis \(The Basics\)](#)")
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SUMMARY AND RECOMMENDATIONS

- **Definition** – Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, severe mucocutaneous reactions triggered, in most cases, by medications and characterized by extensive necrosis and detachment of the epidermis. SJS and TEN exist as a continuum and are classified based on the percentage of skin body surface area (BSA) detached:
 - <10 percent of BSA detached – SJS
 - 10 to 30 percent of BSA detached – SJS/TEN overlap
 - >30 percent of BSA detached – TENHowever, we use the term "SJS/TEN" to refer collectively to SJS, TEN, and SJS/TEN overlap syndrome. (See '[Introduction and classification](#)' above.)
- **Etiology and risk factors** – Medications are the leading trigger of SJS/TEN in both adults and children. [Allopurinol](#), [lamotrigine](#), aromatic anticonvulsants, antibacterial sulfonamides, and "oxicam" or cyclooxygenase-2 (COX-2) inhibitor nonsteroidal anti-inflammatory drugs (NSAIDs) are most commonly implicated ([table 1](#)). Risk factors for SJS/TEN include HIV infection, genetic factors, underlying autoimmune diseases, and malignancy. (See '[Risk factors](#)' above.)
- **Clinical presentation** – SJS/TEN begins with a prodrome of fever and influenza-like symptoms one to three days before the development of mucocutaneous and skin lesions. The cutaneous eruption typically starts with ill-defined, coalescing, erythematous macules with atypical target lesions ([picture 1B-C, 2A-B](#)). As the disease progresses, vesicles and bullae form, and within days the skin begins to slough. Mucosal involvement occurs in approximately 90 percent of cases of SJS/TEN and can precede or follow the skin eruption. (See '[Clinical presentation](#)' above.)
- **Complications** – In severe cases with extensive skin detachment, acute complications may include massive loss of fluids and electrolyte imbalance, hypovolemic shock with renal failure, bacteremia, insulin resistance, hypercatabolic state, and multiple organ dysfunction syndrome. (See '[Extracutaneous involvement and complications](#)' above.)

- **Diagnosis** – The diagnosis of SJS/TEN is based upon clinical and histologic findings in a patient with a history of antecedent drug exposure or febrile illness. Histologic findings on skin biopsy are supportive but not independently diagnostic. (See 'Diagnosis' above.)
-

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Topic 2091 Version 40.0

GRAPHICS

Drugs associated with Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)

Strongly associated*

- Allopurinol
- Lamotrigine
- Sulfamethoxazole
- Carbamazepine
- Phenytoin
- Nevirapine
- Sulfasalazine
- Other sulfonamides
- Oxicam NSAIDs (piroxicam, tenoxicam[¶])
- Phenobarbital
- Etoricoxib[¶]

Associated^Δ

- Diclofenac
- Doxycycline
- Amoxicillin/ampicillin
- Ciprofloxacin
- Levofloxacin
- Amifostine
- Oxcarbazepine
- Rifampin (rifampicin)

Suspected association/lower risk◊

- Pantoprazole
- Glucocorticoids
- Omeprazole
- Tetrazepam[§]
- Dipyrone (metamizole)[¶]
- Terbinafine
- Levetiracetam

Agents are presented in order of decreasing number of cases included in the European Registry (RegiSCAR).

NSAID: nonsteroidal anti-inflammatory drug; RegiSCAR: International Registry of Severe Cutaneous Adverse Reactions.

* Significant association in case-control studies with a lower limit of the confidence interval ≥ 5 and unpublished data from the RegiSCAR.

¶ Etoricoxib, tenoxicam, and dipyrone are NSAIDs available in some countries outside of North America.

Δ Significant association in case-control studies with a lower limit of the confidence interval <5 .

◊ Some cases with plausible causality in medical literature and/or RegiSCAR European Registry.

§ Tetrazepam is a benzodiazepine available in some countries outside North America and Europe.

Data from: The RegiSCAR Project. Available at: <http://www.regiscar.org/index.html> (Accessed on April 4, 2018).

Graphic 91163 Version 11.0

Stevens-Johnson syndrome/toxic epidermal necrolysis: Pharmacogenetic associations in different populations

Associated drug	HLA allele	Population
Carbamazepine	B*1502	Han Chinese, Thai, Malaysian, Singaporean, Indian, Japanese, Korean ^[1-7]
	B*1511	Han Chinese, Japanese, Korean ^[8-9]
	B*5701	European ^[10]
	A*31:01 (for DRESS and SJS/TEN)	European, Japanese, Korean ^[11-13]
Oxcarbazepine	B*1502	Han Chinese, Thai ^[14]
Allopurinol	B*5801	Han Chinese ^[15] European ^[16] Japanese ^[17] Thai ^[18] Korean ^[19]
	B*15:02	Han Chinese, Thai, Malaysian ^[20]
	B*13:01	East Asian ^[21]
	B*51:01	East Asian ^[22]
	B*38:02	Thai ^[23]
Phenytoin	B*15:13	Malaysian ^[24]
	CYP2C9*3	Han Chinese, Japanese, Malaysian, Thai ^[25]
	B*15:02	Han Chinese, Thai ^[20]
	B*38	European ^[10]
	HLA-A*31:01	Korean ^[26]
Dapsone	B*13:01	Southeast Asian ^[27]
Sulfamethoxazole	A*29	European ^[10]
	B*38	
	B*15:02	Thai ^[28]
	C*06-02	Thai ^[28,29]
	C*08:01	Thai ^[30]

Methazolamide	B*59:01	Korean/Japanese/Han Chinese ^[31]
Oxicam NSAIDs	B*73	European ^[10]
Nevirapine	C*04-01	Malawian ^[32]
Strontium ranelate	A*33:03	Han Chinese ^[33,34]

DRESS: drug reaction with eosinophilia and systemic symptoms; HLA: human leukocyte antigen; NSAID: nonsteroidal anti-inflammatory drug; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis.

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Stevens-Johnson syndrome



Vesicles and bullae are characteristic cutaneous findings in Stevens-Johnson syndrome.

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Graphic 76141 Version 7.0

Cutaneous changes of Stevens-Johnson syndrome (SJS)



Generalized eruption of lesions that initially had a target-like appearance but then became confluent, brightly erythematous, and bullous. The patient had extensive mucous membrane involvement and tracheobronchitis.

Reproduced with permission from: Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. In: Color Atlas and Synopsis of Clinical Dermatology: Common and Serious Diseases, 3rd edition, Fitzpatrick TB, Johnson RA, Wolff K, et al (Eds), McGraw-Hill, New York 1997. Copyright © 1997 McGraw-Hill.

Graphic 67632 Version 18.0

Toxic epidermal necrolysis (TEN)



Usually caused by drugs, TEN demonstrates widespread erythema and confluent vesication, leading to sloughing of the skin. Affected patients are at risk for hypernatremic dehydration and sepsis.

*Courtesy of Lee T Nesbitt, Jr. *The Skin and Infection: A Color Atlas and Text*, Sanders CV, Nesbitt LT Jr (Eds), Williams & Wilkins, Baltimore, 1995.*

Graphic 66134 Version 6.0

Toxic epidermal necrolysis



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Diffuse erythema and large areas of denuded epidermis are present.

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Graphic 68458 Version 8.0

Toxic epidermal necrolysis



Multiple bullae and areas of denuded epidermis are present.

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Graphic 59418 Version 10.0

Stevens-Johnson syndrome involving the plantar surface



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Graphic 142092 Version 1.0

Stevens-Johnson syndrome (SJS)



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Multiple erosions and crusts are present on the lips of this patient with SJS.

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Mucosal changes in Stevens-Johnson syndrome/toxic epidermal necrolysis



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Changes similar to those observed in SJS/TEN can also be observed in erythema multiforme majus.

SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis.

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Stevens-Johnson syndrome/toxic epidermal necrolysis



Marked conjunctival injection and discharge in a patient with Stevens-Johnson syndrome/toxic epidermal necrolysis.

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Algorithm of drug causality for epidermal necrolysis (ALDEN)

Criterion	Values	Rules to apply	
Delay from initial drug component intake to onset of reaction (index day)	Suggestive: +3	From 5 to 28 days	-3 to 3
	Compatible: +2	From 29 to 56 days	
	Likely: +1	From 1 to 4 days	
	Unlikely: -1	>56 days	
	Excluded: -3	Drug started on or after the index day In case of previous reaction to the same drug, only changes for: Suggestive: +3, from 1 to 4 days Likely: +1, from 5 to 56 days	
	Definite: 0	Drug continued up to index day or stopped at a time point less than 5 times the elimination half-life* before the index day	
Drug present in the body on index day	Doubtful: -1	Drug stopped at a time point prior to the index day by more than 5 times the elimination half-life* but liver or kidney function alterations or suspected drug interactions¶ are present	-3 to 0
	Excluded: -3	Drug stopped at a time point prior to the index day by more than 5 times the elimination half-life*, without liver or kidney function alterations or suspected drug interactions¶	
	Positive specific for disease and drug: 4	SJS/TEN after use of same drug	
Prechallenge/rechallenge	Positive specific for disease or drug: 2	SJS/TEN after use of similar ^Δ drug or other reaction with same drug	-2 to 4
	Positive unspecific: 1	Other reaction after use of similar ^Δ drug	
	Not done/unknown: 0	No known previous exposure to this drug	

	Negative: -2	Exposure to this drug without any reaction (before or after reaction)	
Dechallenge	Neutral: 0	Drug stopped (or unknown)	-2 or 0
	Negative: -2	Drug continued without harm	
Type of drug (notoriety)	Strongly associated: 3	Drug of the "high-risk" list according to previous case-control studies	-1 to 3
	Associated: 2	Drug with definite but lower risk according to previous case-control studies	
	Suspected: 1	Several previous reports, ambiguous epidemiology results (drug "under surveillance")	
	Unknown: 0	All other drugs including newly released ones	
	Not suspected: -1	No evidence of association from previous epidemiology study with sufficient number of exposed controls ^Δ	
		Intermediate score = total of all previous criteria	
Other cause	Possible: -1	Rank all drugs from highest to lowest intermediate score	-1
		If at least 1 has an intermediate score >3, subtract 1 point from the score of each of the other drugs taken by the patient (another cause is more likely)	

Final score: -12 to 10

The likelihood of a patient having SJS/TEN is based on the final score:

- Score <0 — Very unlikely
- Score 0 to 1 — Unlikely
- Score 2 to 3 — Possible
- Score 4 to 5 — Probable
- Score ≥6 — Very probable

SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; ATC: anatomical therapeutic chemical.

* Drug (or active metabolite) elimination half-life from serum and/or tissues (according to pharmacology textbooks), taking into account kidney function for drugs predominantly cleared by kidney and liver

function for those with high hepatic clearance.

¶ Suspected interaction was considered when more than 5 drugs were present in a patient's body at the same time.

Δ Similar drug = same ATC code up to the fourth level (chemical subgroups).

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Graphic 93517 Version 6.0

Target lesions of erythema multiforme



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Target lesions with central bullae are present on the hand.

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Erythema multiforme



Multiple acrally distributed target lesions and mucosal erosions are present in this patient with erythema multiforme majus.

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Erythema multiforme



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Multiple erythematous plaques with dusky centers are present on the arms of this patient with erythema multiforme.

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Exanthematous (morbilloform) drug eruption



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Numerous small, discrete papules on the back of a patient with exanthematous drug eruption.

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Exanthematous (morbilloform) drug eruption



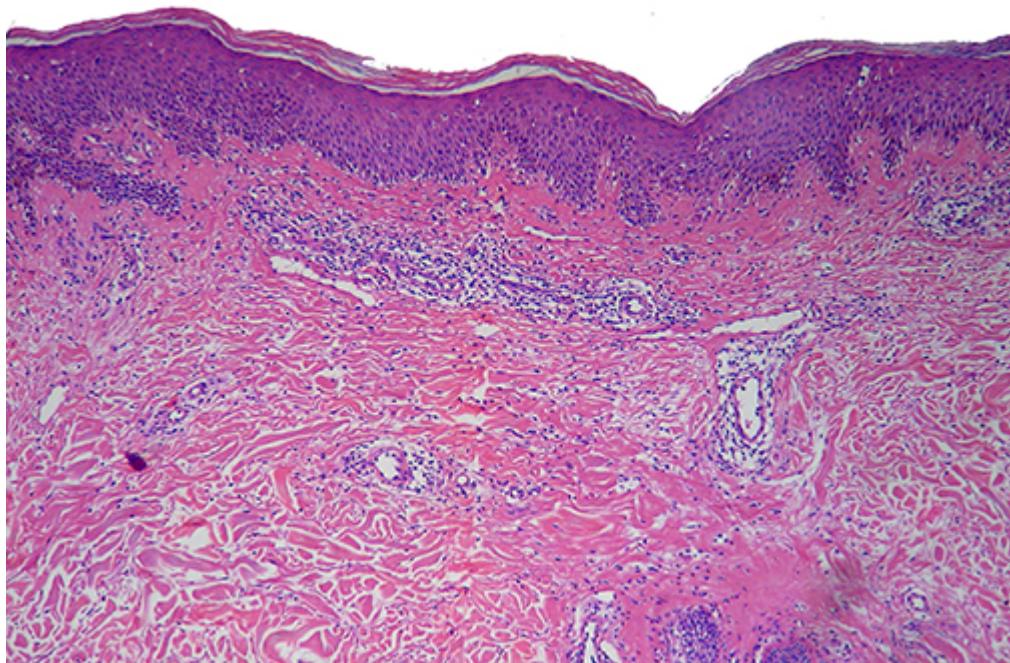
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Numerous erythematous macules and papules are present in this child with a morbilliform drug eruption.

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Histopathologic features of exanthematous (morbilliform) drug eruption



The histologic features of morbilliform drug eruptions are typically those of an interface dermatitis with scattered, dyskeratotic keratinocytes along the dermoepidermal junction. There is also a superficial, perivascular, lymphocytic infiltrate with scattered eosinophils and mild papillary edema.

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Graphic 86550 Version 6.0

Clinical and laboratory features of severe drug eruptions

Syndrome	Rash morphology	Localization	Timing	Internal organ involvement	Systemic signs	Lab findings
DRESS	Maculopapular exanthem Erythroderma Facial edema Purpura, pustules	Generalized Mucosal involvement infrequent	2 to 6 weeks	Lymphadenopathy Hepatitis Pneumonitis Nephritis Thyroiditis Myocarditis Eosinophilia	Fever (>38°C/100.4°F) Malaise Fatigue	Eosinophilia Atypical lymphocytes Abnormal liver function
AGEP	Intertriginous erythema, maculopapular exanthem, widespread nonfollicular pinpoint pustules	Generalized, rarely flexural Mucosal involvement rare	1 to 11 days	Liver, renal, pulmonary may be involved but generally mild	Fever (>38°C/100.4°F)	Leukocytosis with neutrophilia (>70%)
SJS/TEN	Dusky red confluent erythema, atypical target lesions, purpura, blisters, and sheet-like detachment Nikolsky sign is positive SJS <10%, SJS/TEN 10 to 30%, TEN >30%	Disseminated Mucosal involvement nearly in all cases	4 to 28 days	Pneumonitis, hepatitis, acute renal failure, GI, leucopenia	Fever (>38°C/100.4°F) Malaise Fatigue Sore throat Dysphagia, photophobia	Lymphopenia Epicutaneous necrosis with thickening of epidermis

AGEP: acute generalized exanthematous pustulosis; DRESS: drug reaction with eosinophilia and systemic symptoms; GI: gastrointestinal; SJS/TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis.

Adapted from:

1. Scherer K, Bircher A. Adverse drug reactions and the skin--from trivial to fire signal. Internist (Berl) 2009; 50:171.

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Graphic 86557 Version 8.0

Acute generalized exanthematous pustulosis (AGEP)



Confluent nonfollicular pustules superimposed on edematous erythema in a 46-year-old woman with AGEP. A skin biopsy showed intracorneal pustules with numerous neutrophils and neutrophilic infiltration of the epidermis and upper dermis.

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Reactive infectious mucocutaneous eruption (RIME)



Typical oral edema, ill-defined erosions, and crusting in a patient with RIME.

RIME: reactive infectious mucocutaneous eruption.

Graphic 126081 Version 2.0

Paraneoplastic pemphigus



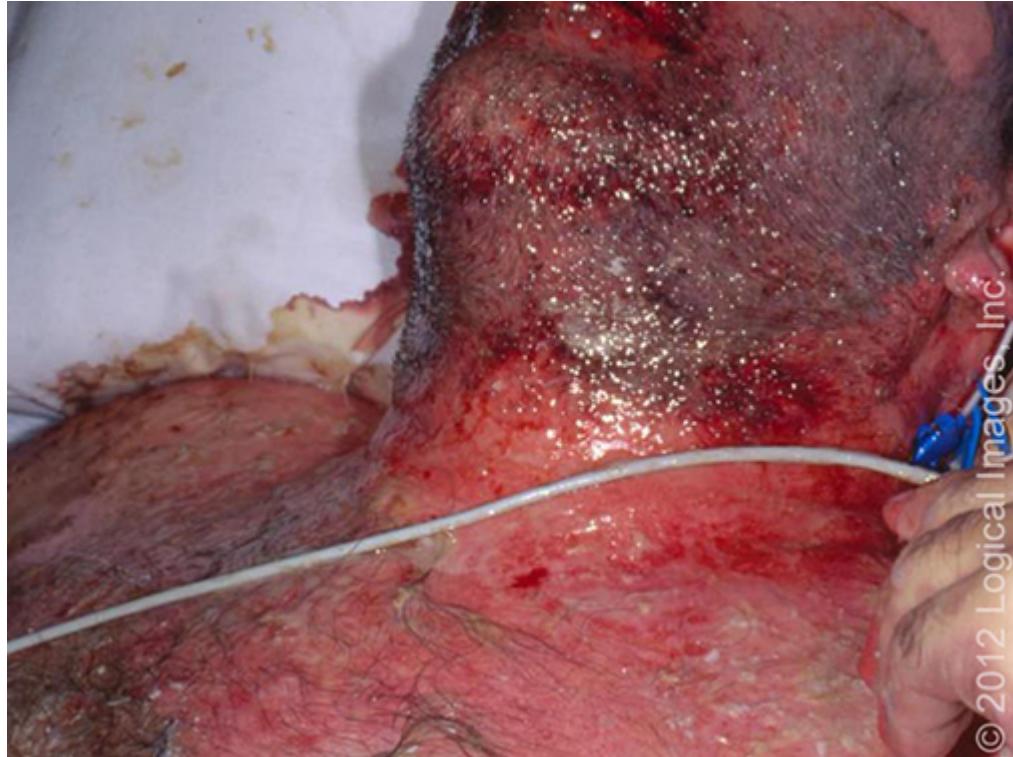
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Vesicles and flaccid bullae are present on the skin.

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Paraneoplastic pemphigus



Widespread skin sloughing and erosions in paraneoplastic pemphigus.

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Graphic 62146 Version 5.0

Paraneoplastic pemphigus

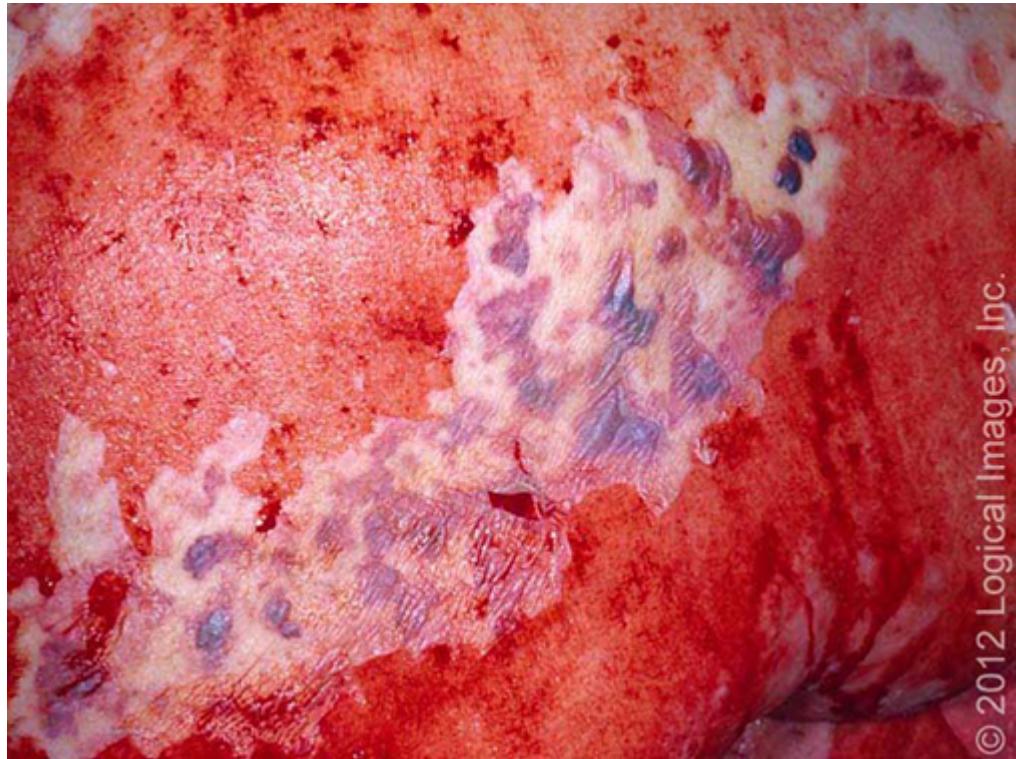


An erosive mucositis in a patient with paraneoplastic pemphigus associated with Castleman's tumor; mucous membrane and cutaneous lesions cleared with tumor removal.

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Linear IgA bullous dermatosis resembling toxic epidermal necrolysis



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Extensive bullae and skin sloughing are present.

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