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A Compilation of Drug Etiologies of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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Abstract

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are adverse reactions that affect the mucocutaneous surfaces by causing necrosis and detachment of the epidermis. The difference between SJS and TEN is in the percentage of the body surface area (BSA) affected. TEN is known to affect greater BSA than SJS. The pathogenesis of SJS/TEN is attributed to drug-specific cell-mediated cytotoxic reactions that directly and indirectly lead to keratinocyte apoptosis through mediators. Clinical presentation begins with influenza-like symptoms, with the disease affecting the skin, oral, ocular, and urogenital regions most frequently. Although SJS/TEN is mainly due to various drugs, infection and vaccination can also induce SJS/TEN. This review outlines a compilation of all drugs implicated in SJS/TEN cases based on studies, mainly in case reports and other study types. Drug classes implicated in SJS/TEN cases include antibiotics, anticonvulsants, antineoplastics, analgesics, and diuretics, among others. There is no fully established diagnostic modality for SJS/TEN; treatment is done mainly by withdrawing the offending agent. In addition to withdrawing the offending agent, a multidisciplinary care team is essential in managing these patients. Several pharmacologic modalities have also been proposed in treatment, but there is still insufficient evidence for the efficacy of one against the other.

Categories: Internal Medicine, Dermatology, Allergy/Immunology

Keywords: toxic epidermal necrolysis, stevens-johnson syndrome (sjs), stevens-johnson syndrome, sjs/ten overlap, etiologies, drugs, toxic epidermal necrolysis (ten)

Introduction And Background

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are adverse reactions that affect the mucocutaneous surfaces, causing necrosis and detachment of the epidermis. SJS and TEN are known to be on a similar disease spectrum, with the difference being the amount of body surface area (BSA) affected. SJS affects less than 10% of the BSA, while TEN affects greater than 30% of the BSA [1]. It is classified as SJS/TEN overlap when 10-30% of BSA is affected [1]. In this review, we will use SJS/TEN to refer to the full spectrum of the adverse reactions to the disease.

The incidence of SJS/TEN varies, but it is extremely low. In the UK, the incidence of SJS/TEN was 5.76 cases per million per year [2]. In France, TEN incidences were 1.2-1.3 cases per million per year [3]. The incidence of SJS/TEN can be estimated to be between two to seven cases per million people per year [4]. Females tend to be more affected than males, with a female-to-male ratio of 2:1 [5]. There is also a higher incidence of SJS/TEN among patients with HIV and cancer. Incidences of SJS/TEN among HIV patients have been reported to be between 0.95 and one per 1000 individuals with HIV [6]. The increased incidence in HIV patients is suspected because of the multiple medications used, immune dysregulation, genetic polymorphisms, and infections. Mortality for SJS/TEN ranges from 10% to 50%, with more mortality associated with TEN than with SJS [7].

In addition to HIV and cancer, genetic predispositions also put one at risk for having SJS/TEN. Patients with human leukocyte antigen (HLA)-B*15:02 and HLA-B*15:11 have an increased risk of SJS/TEN with carbamazepine use, especially in Asian populations [8-9]. HLA-B*58:01 has been implicated with allopurinol-induced SJS/TEN in Asian and non-Asian populations [10]. Other HLA alleles that have been implicated with other drugs include HLA-A*31:01, HLA-A*24:02, and HLA-B*13:01 [11-13]. Genetic polymorphisms in the CYP2C19 gene coding for the cytochrome P450 isoform may also increase the risk of SJS/TEN with drugs like phenobarbital, phenytoin, or carbamazepine [14].

Review

Pathogenesis

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The pathogenesis of SJS/TEN has yet to be understood entirely. Research has shown that SJS/TEN is due to a cell-mediated cytotoxic reaction through a CD8+ cell that leads to keratinocyte apoptosis. These cell-mediated T-cell reactions are drug-specific and directed against the native form of the drug. It is proposed that the different drugs that cause SJS/TEN bind with the major histocompatibility complex (MHC) class I and T-cell receptors (TCR) and lead to the expansion of drug-specific cytotoxic T cells that cause keratinocyte apoptosis both directly and indirectly through the release of cell mediators [15].

As noted, keratinocyte apoptosis is caused by cytotoxic mediated reactions through drug-specific CD8+ cytotoxic cells and natural killer (NK) cells directly and indirectly through mediators. Some of the mediators that have been proposed for these reactions include Fas-ligand, tumor necrosis factor (TNF)-alpha, perforin/granzyme, TNF-related apoptosis-inducing ligand (TRAIL), and granulysin. Granulysin, primarily known to be produced by cytotoxic T-cells and NK cells, has been majorly implicated in SJS/TEN. In a study, granulysin was the most highly expressed cytotoxic molecule through gene expression in SJS/TEN patients. The level of granulysin in blister fluid has also been correlated with the severity of SJS/TEN. When granulysin was decreased, the cytotoxicity was also decreased [16]. Another mediator implicated in SJS/TEN is interleukin-15 (IL-15). IL-15 is known to increase in SJS/TEN and has been correlated with disease severity and hospital inpatient mortality [17].

Other studies have also pointed out necroptosis contributes to keratinocyte death in SJS/TEN. The necroptosis process occurred because of the annexin A1 produced by monocytes binding to formyl peptide receptor 1 (FRP-1), leading to SJS/TEN [18].

Clinical presentation

SJS/TEN often begins with a prodromal nonspecific symptom that looks like influenza. Symptoms include fever often greater than 38°C, malaise, odynophagia, photophobia, and conjunctival injection. Sometimes, skin involvement is the first manifestation of the disease, occurring with blistering or skin tenderness. Early stages of SJS/TEN cutaneous lesions begin with poorly defined erythematous macules with purpuric centers or diffuse erythema, which could be tender to touch. The lesions are often symmetric and spare the scalp, palm, and soles of the body. It often begins at the face and then spreads to the thorax. It often exhibits a positive Nikolsky sign (slippage of the top layer of the skin from the bottom layer when rubbed). As the disease progresses, vesicles and bullae form on the skin, which later slough off. The degree of skin involvement based on total body surface area (TBSA) is a marker of the disease's severity, so it should be assessed regularly. Mucosal involvement, generally oral, ocular, and urogenital, often occurs in about 90% of patients [19]. Ocular involvement often includes conjunctivitis with purulent discharge, corneal ulceration, anterior uveitis, panophthalmitis, and trichiasis. The acute phase of SJS/TEN lasts for eight to 12 days, affecting the mucous membrane and causing denuded skin. Re-epithelization begins after several days and takes two to four weeks to form [20].

Chronic progression of the disease leads to multiple organ damage. For the skin, it can result in hypo/hyperpigmentation, scarring, and chronic pruritus. Ocular involvement includes dry eyes, symblepharon, corneal scarring, and rarely blindness. Long-term urogenital complications include adhesion formation, urethral stenosis, scarring, and strictures. Bronchiectasis, obstructive disorders, and chronic bronchitis/bronchiolitis are common presentations for the pulmonary system. In addition, long-term psychiatric consequences such as anxiety, depression, and post-traumatic stress disorder have been reported [21].

Due to extensive skin detachment, acute complications include massive fluid loss, infections, electrolyte imbalance, hypovolemic shock with renal failure, pulmonary complications (pneumonia, interstitial pneumonitis), gastrointestinal complications, and disseminated intravascular complications (DIC).

Drug etiologies associated with SJS/TEN

The cause of SJS/TEN is most often due to drugs. It takes approximately four weeks of continuous medication use for SJS/TEN to develop. Additionally, infections like *Mycoplasma pneumoniae* and herpes simplex virus have been associated with SJS/TEN. Although rare, SJS/TEN has also been reported after vaccinations, especially in childhood [22]. In one-third of cases of SJS/TEN, the causes are idiopathic. This paper records a compilation of the drugs that have caused SJS/TEN. Table 1 below shows the classification of the medications that have caused SJS/TEN.

Drug classification	References
Antibiotics	[23-45]
Anticonvulsants	[46-55]
Benzodiazepines	[56-59]
Non-benzodiazepines	[60]
Sulfonylureas	[24,61,62]
Diuretics	[63-69]
Analgesics	[4,70-74]
Antidepressants	[75-80]
Xanthine oxidase inhibitors	[81]
Androgenic hormones	[82,83]
Antineoplastics	[84-99]
Immunosuppressants/immunomodulators	[100]
Corticosteroids	[101]
Antiparasitic drugs	[102,103]
Antiviral drugs	[104-110]
Antifungal drugs	[111]
Aggrenox	[112]
Antihistamines	[113]
Angiotensin-converting enzyme inhibitors & angiotensin receptor blockers	[114,115]
Aminosalicylates	[116]
Others	[35,117-121]

TABLE 1: Drugs reported to induce SJS/TEN.

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

Antibiotics

Antibiotics are one of the classes of drugs that have been implicated in SJS/TEN. Among the antibiotics, sulfonamides are the ones that have been most implicated. The most common sulfonamide that causes SJS/TEN is trimethoprim-sulfamethoxazole (cotrimoxazole). Attached in Table 2 is a list of common antibiotics implicated in SJS/TEN.

Antibiotic class	Antibiotics	References
Sulfonamides	Trimethoprim-sulfamethoxazole (cotrimoxazole) and sulfasalazine	[23-25]
Aminopenicillin	Amoxicillin/clavulanic acid, ampicillin, ampicillin-sulbactam	[26]
Fluoroquinolones	Ciprofloxacin, norfloxacin, and levofloxacin	[27-30]
Tetracyclines	Tetracycline, minocycline, doxycycline	[31-33]
Macrolides	Azithromycin, clarithromycin, erythromycin, roxithromycin, telithromycin	[34-37]
Cephalosporins	Cefepime, cefixime, cefuroxime, cefazolin and ceftriaxone	[35,38-40]
Other	Metronidazole, rifampin, clindamycin, vancomycin, nitrofurantoin	[41-45]

TABLE 2: Antibiotics that have been associated with SJS/TEN cases.

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

Anticonvulsants/Antiepileptics Drugs

Anticonvulsants have also been implicated majorly in causing SJS/TEN. Various alleles have been suspected to be associated with some antiepileptic drugs (AEDs) in causing SJS/TEN. Carbamazepine-induced SJS/TEN is associated with the HLA-B*1502 allele [\[46\]](#). Oxcarbazepine was involved with HLA-B*1518 in another report on causing SJS/TEN [\[47\]](#). In addition, another study implicated combinatorial AEDs that are more likely to cause SJS/TEN. Table [3](#) below illustrates some of the AEDs associated with SJS/TEN.

Classification	Anticonvulsants/AEDs	References
Older drugs	Phenytoin, valproic acid, carbamazepine, phenobarbital	[46,48]
Newer drugs	Lamotrigine, oxcarbazepine, zonisamide, rufinamide, clorazepate, eslicarbazepine, clonazepam, and levetiracetam	[47,49-54]
Combination drugs	Clobazam-gabapentin, phenytoin-gabapentin, valproic acid-gabapentin, clobazam-clonazepam, clobazam–valproic acid, fosphenytoin-lamotrigine, and lacosamide-levetiracetam	[55]

TABLE 3: Common anticonvulsants that have been implicated in SJS/TEN.

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

Benzodiazepines/Non-benzodiazepines

Benzodiazepines and non-benzodiazepines, which are used to treat many conditions, have also been implicated in SJS/TEN. Chlormezanone was discontinued worldwide in 1996 due to severe and rare side effects of TEN. Table [4](#) highlights the drugs in these categories implicated in SJS/TEN.

Classification	Drugs	References
Benzodiazepines	Tetrazepam, chlordiazepoxide, clobazam, flurazepam	[56-59]
Non-benzodiazepines	Chlormezanone	[60]

TABLE 4: Benzodiazepines/non-benzodiazepines implicated in SJS/TEN.

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

Sulfonylureas

Some case reports have implicated glipizide and glimepiride in SJS/TEN [61,62]. However, European case-control studies have denied any significant risk of SJS/TEN with the use of sulfonylureas [24].

Diuretics

Table 5 lists some diuretic medications that have been implicated with SJS/TEN. Other case-control studies, however, do not believe there is a significant risk of SJS/TEN with diuretics [63,64].

Classification	Drugs	References
Loop diuretics	Furosemide, torsemide	[65-67]
Thiazide	Metolazone	[63]
Potassium-sparing diuretics	Spironolactone	[64]
Carbonic-anhydrase inhibitors	Acetazolamide, methazolamide, dorzolamide, and brinzolamide	[68,69]

TABLE 5: Diuretics that have been implicated in SJS/TEN.

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

Analgesics

Some analgesics have been associated with SJS/TEN. This is often common with nonsteroidal anti-inflammatory drugs (NSAIDs). A study that examined a total of 1,868 reports of SJS adverse events associated with five NSAIDs showed that ibuprofen had the highest association with SJS. Ibuprofen also had the highest rate of hospitalization but the lowest fatality rate [70]. Table 6 below lists the NSAIDs implicated in SJS/TEN cases.

NSAIDs classification	Drugs	Reference
Non-selective COX inhibitors	Diclofenac, ibuprofen, aspirin, piroxicam, naproxen, ketoprofen, tenoxicam	[71,72]
Preferential COX-2 inhibitors	Etodolac	[4]
Selective COX-2 inhibitors	Rofecoxib, celecoxib, etoricoxib,	[70]
Analgesic-antipyretic with poor anti-inflammatory action	Acetaminophen	[73,74]

TABLE 6: NSAIDs implicated in SJS/TEN.

SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; NSAIDs: nonsteroidal anti-inflammatory drugs; COX: cyclooxygenase.

Antidepressants

Antidepressants, which are commonly used to treat depression, have also been associated with inducing SJS/TEN. Table 7 lists some common antidepressants associated with SJS/TEN cases.

Classification	Drugs	Reference
Selective serotonin reuptake inhibitors (SSRIs)	Sertraline, fluoxetine	[75-77]
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Duloxetine	[78,79]
Atypical antidepressants	Mirtazapine	[80]

TABLE 7: Antidepressants that have been associated with SJS/TEN cases.

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

Xanthine Oxidase Inhibitors

Allopurinol, a drug used in the first-line treatment of gout, is a common cause of SJS/TEN. A particular case of a 33-year-old male diagnosed with gout and subsequently started on allopurinol began to demonstrate symptoms of TEN after 10 days of use. The patient was also found to test positive for HLA-B*5801 [81]. It is important to note that this allele has been associated with SJS/TEN cases with allopurinol use.

Androgenic Hormones

Androgenic anabolic steroids: SJS was reported in the case of a 41-year-old patient abusing anabolic steroids. The patient had been participating in competitive bodybuilding for roughly 20 years while taking varying doses of anabolic androgenic steroids (AAS). Further, the case confirms that the patient was not on other medications besides AAS [82].

Danazol: Other androgenic drugs include danazol, which is like testosterone and can be used to treat endometriosis. Additionally, danazol has been approved as a second-line agent for treating hematologic disorders related to SLE, including thrombocytopenia. Danazol has been implicated in triggering SJS [83].

Antineoplastics Drugs

Many antineoplastic drugs have been associated with SJS/TEN cases, as shown in Table 8. SJS/TEN is also common when antineoplastics are combined. Among the combined antineoplastics that have been implicated are docetaxel/cyclophosphamide, tegafur/gimeracil/oteracil (TS-1), brentuximab vedotin, and enfortumab vedotin [84-86]. In some instances, combination therapy between ipilimumab (which targets CTLA-4) and a programmed cell death protein 1 (PD-1) inhibitor resulted in SJS/TEN [87,88].

Classification	Drugs	References
Taxanes	Paclitaxel, docetaxel	[89,90]
Hormonal agents	Tamoxifen, enzalutamide	[91-93]
Protein kinase inhibitors	Ribociclib, afatinib, erlotinib, gefitinib, vandetanib, imatinib, sorafenib, bortezomib, vemurafenib	[94,95]
Monoclonal antibodies	Cetuximab, panitumumab, rituximab, ipilimumab, pembrolizumab, atezolizumab, nivolumab	[94,96]
Alkylating agents	Treosulfan, chlorambucil, mechlorethamine, temozolomide, bendamustine, procarbazine	[97]
Topoisomerase inhibitors	Etoposide	[97]
Antibiotics, cytotoxic	Anthracycline, doxorubicin	[97]
Antimetabolites	Methotrexate, cytarabine, fludarabine, gemcitabine, capecitabine, cladribine-6, mercaptopurine, pralatrexate, pemetrexed	[97]
Biologic response modifiers	Aldesleukin, denileukin	[97]
Miscellaneous	Thalidomide, lenalidomide	[98,99]

TABLE 8: Antineoplastics that have been associated with SJS/TEN.

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

Immunosuppressants/Immunomodulators

Mizoribine: This immunosuppressant is used to treat renal transplant patients, systemic lupus erythematosus (SLE), lupus nephritis, and several childhood nephrotic syndromes such as IgA nephropathy. It has been implicated in one case of SJS, which occurred in a 32-year-old Japanese woman after receiving mizoribine for treating SLE with lupus nephritis for six months [100].

Corticosteroids

Corticosteroids are a mainstay in treating patients with early-stage SJS/TEN. However, it is crucial to know that administering high-dose corticosteroids in certain patients may paradoxically induce SJS/TEN. Some of these patient conditions may act as predisposing factors, including collagen disease, autoimmune disorders, or brain tumors [101].

Antiparasitic Drugs

Albendazole: Albendazole is an antiparasitic drug that can treat hydatid disease and other infections caused by tapeworms. A case report details albendazole causing TEN in a 16-year-old female [102].

Ivermectin: An antiparasitic drug that is FDA-approved to treat a variety of internal nematode infections has been documented in several reports of SJS/TEN [103]. Therefore, its implication in this severe adverse effect is crucial to be aware of. It is also important to mention that although not FDA-authorized or approved, its use has rapidly increased recently as COVID-19 prevention and as a component of the COVID-19 treatment cocktail.

Antiviral Drugs

Antivirals have also been associated with SJS/TEN cases, as noted in Table 9. HIV patients are known to be at higher risk than the rest of the population from developing SJS/TEN.

Classification	Drugs	References
Neuraminidase inhibitor	Oseltamivir	[104]
Nucleoside reverse transcriptase inhibitor (NRTI)	Adefovir and tenofovir	[105,106]
Non-nucleoside reverse transcriptase inhibitor (NNRTI)	Nevirapine & efavirenz	[107-109]
Synthetic nucleoside analog	Acyclovir	[110]

TABLE 9: Antivirals that have been implicated with SJS/TEN cases.

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

Antifungal

Terbinafine: In one case, terbinafine was known to induce SJS/TEN overlap. The likelihood of this association is weak but possible [\[111\]](#).

Aggrenox

Aggrenox is a combination drug of acetylsalicylic acid (aspirin) and dipyridamole, which works to inhibit platelet activation and is thus used as an anticoagulant often to reduce the risk of stroke in high-risk patients. At least one case of Aggrenox-induced SJS has been reported. One occurred in a 74-year-old Chinese woman who was switched from aspirin to Aggrenox after she had experienced a transient ischemic attack (TIA) despite treatment with aspirin. She developed acute-onset progressive SJS within 24 hours from the first dose [\[112\]](#).

Antihistamines

A case of SJS/TEN overlap induced by fexofenadine-pseudoephedrine (Telfast-D) was reported in a middle-aged woman on treatment for persistent allergic rhinitis and sinusitis. Fexofenadine, an antihistamine sold under the brand name Allegra, is an over-the-counter drug used to treat allergy symptoms. After two doses, she initially presented with a swollen lip, which progressed to diffuse blistering with a positive Nikolsky sign over the week. She was ultimately diagnosed with SJS/TEN [\[113\]](#).

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

These drugs are rarely reported to be associated with causing SJS/TEN. However, one report mentions the onset of SJS in a patient after being recently prescribed ramipril for hypertension [\[114\]](#). Another case implicated losartan, an angiotensin receptor blocker (ARB), in causing SJS in a geriatric patient with renal impairment [\[115\]](#).

Aminosalicylates

Mesalamine and sulfasalazine, which are known aminosalicylates, have been found to have a causal association with causing SJS/TEN. The estimated absolute risk of four cases per 100,000 users was found to develop SJS/TEN [\[116\]](#).

Other causes that have been implicated in SJS/TEN cases

Acetylcysteine

Acetylcysteine is an antioxidant and glutathione inducer that is utilized for the treatment of acetaminophen overdose. It has been implicated in a reported case of SJS [\[35\]](#).

Ursodeoxycholic Acid

A drug used in the treatment of primary biliary cholangitis, as well as various other cholestatic disorders, has also been rarely implicated in cases of SJS/TEN. One ursodeoxycholic acid (UDCA)-induced SJS/TEN case occurred in a 24-year-old female patient being treated for deranged liver function tests. However, it should be noted that she was also prescribed concomitant omeprazole and domperidone, which also could have contributed to the induction of the severe cutaneous reaction [\[117\]](#).

Strontium Ranelate

The anti-osteoporotic agent boasts an excellent safety profile, aside from several cases of inducing SJS/TEN. In one case, strontium ranelate triggered what was diagnosed as mild SJS with a good prognosis in a 70-year-old woman after one month of beginning drug use. Although classified as mild, she exhibited multiple itching erythematous macules and plaques, which progressed to involve the entire body with severe oral and ocular mucosa involvement. Overall, early diagnosis and treatment led to a good prognosis in this patient. Thus, this adverse effect should be considered with this drug use [118].

Other non-therapeutic agents/chemicals in the etiology of SJS include iodine contrast, iopentol, commercial cannabinoid oil, and carbamate [119-121].

Diagnosis and diagnostic markers

There are currently no established diagnostic criteria for SJS/TEN. Diagnosis begins with suspicion in those with fever, flu-like symptoms, or SJS/TEN skin-like changes recently exposed to any drug or offending agent that could have triggered it. Usually, it takes one to four weeks of drug use before developing SJS/TEN symptoms [122]. Skin biopsy could be done through a punch or deep shave biopsy to confirm the diagnosis and exclude other diagnoses. Early histopathologic changes will show apoptotic keratinocytes in the basal layer of the epidermis, along with a perivascular mononuclear inflammatory infiltrate composed primarily of T lymphocytes in the papillary dermis [4,123]. This infiltrate is not diagnostic and could be seen in other skin conditions. Direct immunofluorescence is always negative for SJS/TEN.

Assessment of the likely drug causality is vital in diagnosis, as early withdrawal of the offending agent is a good prognostic factor. Detailed history and clinical insight are required to pinpoint the offending agent that could have triggered the process. An algorithm of drug causality for epidermal necrolysis (ALDEN) has been created to assess drug causality, especially in those taking multiple drugs. The ALDEN score is based on six factors (time lag from initial drug intake to onset of reaction; the probability that the drug was present in the body at the onset of reaction; pre-challenge (administration of the same drug to the patient in the past)/rechallenge; dechallenge; type of drug (notoriety); other possible etiologic alternatives) [124]. The final score is from -12 to 10, and a score is assigned to each medication. The grading system notes ≥ 6 as very probable, 4 to 5 as probable, 2 to 3 as possible, 0 to 1 as unlikely, and ≤ 0 as unlikely.

Recent research is looking for diagnostic markers to aid in diagnosing SJS/TEN. Markers that have been considered in research include the rapid granulysin test, CCR7, RIP3, galectin-7, granzyme B, and interferon gamma (IFN- γ) [125,126]. However, diagnostic markers have yet to be fully established as the main diagnosis marker. Differential diagnoses to consider and rule out when diagnosing SJS/TEN include erythema multiforme, acute generalized exanthematous pustulosis, phototoxic eruptions, and staphylococcal scalded skin syndrome.

Management

The first step in the management of SJS/TEN is dependent on the etiology of the disease. In infectious cases, treatment of the infection is essential. If drugs are the cause, withdrawal of the offending agent or drug is vital as prompt withdrawal decreases mortality [127]. As noted earlier, it takes about one to four weeks of continuous drug use for SJS/TEN to develop, so the exact temporal relationship of drug use must be considered when identifying the suspect drug. The ALDEN score is also an important tool that helps identify suspicious drugs, especially when multiple drug use occurs. Another crucial prognostic tool is the severity of illness score for TEN (SCORTEN). It is based on seven independent risk factors and is often used to predict mortality for SJS/TEN. The score should be analyzed within 24 hours of admission and on day three of the presentation [128].

After dealing with the primary source of the disease, the main treatment modality is supportive. A multidisciplinary care team is essential as SJS/TEN affects various organs. Regarding the skin, wound care of patients is vital in preventing further infection or complications. Wound care could be achieved through conservative means (the epidermis is left in place, and further non-adhesive dressing is used to help in healing) or surgical means (the affected epidermis is removed, and biologic membrane of xenografts, allograft, biosynthetic dressings may be added or not). No evidence exists for surgical management of wounds above conservative means [129]. Other supportive management is fluid replacement to prevent organ hypoperfusion, temperature management to prevent hypothermia, nutritional support through oral means or nasogastric tube if the oral membrane is affected, pain control, infection prevention, and ventilatory support in cases of acute hypoxic respiratory failure, and urogenital and ocular care.

Several pharmacologic modalities have been proposed to treat SJS/TEN. Some are systemic corticosteroids, intravenous immunoglobulin (IVIG), cyclosporine, plasmapheresis, and anti-TNF agents. Some evidence has shown both positive and negative plausibility to their use [125]. However, there is still insufficient evidence for the efficacy of one against the other.

Conclusions

In conclusion, SJS/TEN are often adverse reactions that affect the skin and mucous membranes of the mouth, eyes, and urogenital region. The difference between SJS and TEN is in the percentage of BSA affected. The pathogenesis of SJS/TEN is due to a cell-mediated cytotoxic reaction that leads to keratinocyte apoptosis through direct and indirect mediators. A major mediator that has been implicated is granulysin. Drugs often cause SJS/TEN, but other etiologies like infections have been suggested. One-third of cases of SJS/TEN are also known to be from idiopathic causes. There is no established diagnostic modality regarding diagnosis, but apoptotic keratinocytes with inflammatory infiltrate are the key findings. Management of SJS/TEN is generally the removal of the precipitating agent and supportive treatment.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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References

1. Roujeau JC: Stevens-Johnson syndrome and toxic epidermal necrolysis are severity variants of the same disease which differs from erythema multiforme. *J Dermatol.* 1997, 24:726-9. [10.1111/j.1346-8138.1997.tb02524.x](https://doi.org/10.1111/j.1346-8138.1997.tb02524.x)
2. Frey N, Jossi J, Bodmer M, Bircher A, Jick SS, Meier CR, Spöndlin J: The epidemiology of Stevens-Johnson syndrome and toxic epidermal necrolysis in the UK. *J Invest Dermatol.* 2017, 137:1240-7. [10.1016/j.jid.2017.01.031](https://doi.org/10.1016/j.jid.2017.01.031)
3. Roujeau JC, Guillaume JC, Fabre JP, Penso D, Fléchet ML, Girre JP: Toxic epidermal necrolysis (Lyell syndrome). Incidence and drug etiology in France, 1981-1985. *Arch Dermatol.* 1990, 126:37-42. [10.1001/archderm.126.1.37](https://doi.org/10.1001/archderm.126.1.37)
4. Stevens-Johnson syndrome and toxic epidermal necrolysis: pathogenesis, clinical manifestations, and diagnosis. (2022). Accessed: November 5, 2022: [https://www.uptodate.com/contents/stevens-johnson-syndrome-and-toxic-epidermal-necrolysis-pathogenesis-clinical-manif....](https://www.uptodate.com/contents/stevens-johnson-syndrome-and-toxic-epidermal-necrolysis-pathogenesis-clinical-manif...)
5. Sekula P, Dunant A, Mockenhaupt M, et al.: Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. *J Invest Dermatol.* 2013, 133:1197-204. [10.1038/jid.2012.510](https://doi.org/10.1038/jid.2012.510)
6. Mittmann N, Knowles SR, Koo M, Shear NH, Rachlis A, Rourke SB: Incidence of toxic epidermal necrolysis and Stevens-Johnson syndrome in an HIV cohort: an observational, retrospective case series study. *Am J Clin Dermatol.* 2012, 13:49-54. [10.2165/11593240-000000000-00000](https://doi.org/10.2165/11593240-000000000-00000)
7. Fakoya AO, Omenyi P, Anthony P, Anthony F, Etti P, Othiniyi DA, Olunu E: Stevens-Johnson syndrome and toxic epidermal necrolysis; extensive review of reports of drug-induced etiologies, and possible therapeutic modalities. *Open Access Maced J Med Sci.* 2018, 6:730-8. [10.3889/oamjms.2018.148](https://doi.org/10.3889/oamjms.2018.148)
8. Tangamornsuksan W, Chaikunapruk N, Somkruea R, Lohitnavy M, Tassaneeyakul W: Relationship between the HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *JAMA Dermatol.* 2013, 149:1025-32. [10.1001/jamadermatol.2013.4114](https://doi.org/10.1001/jamadermatol.2013.4114)
9. Wang Q, Sun S, Xie M, Zhao K, Li X, Zhao Z: Association between the HLA-B alleles and carbamazepine-induced SJS/TEN: a meta-analysis. *Epilepsy Res.* 2017, 135:19-28. [10.1016/j.eplepsyres.2017.05.015](https://doi.org/10.1016/j.eplepsyres.2017.05.015)
10. Somkruea R, Eickman EE, Saokaew S, Lohitnavy M, Chaikunapruk N: Association of HLA-B*5801 allele and

- allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *BMC Med Genet*. 2011, 12:118. [10.1186/1471-2350-12-118](https://doi.org/10.1186/1471-2350-12-118)
11. Tempark T, Satapornpong P, Rerknimitr P, et al.: Dapsone-induced severe cutaneous adverse drug reactions are strongly linked with HLA-B*13: 01 allele in the Thai population. *Pharmacogenet Genomics*. 2017, 27:429-37. [10.1097/FPC.0000000000000306](https://doi.org/10.1097/FPC.0000000000000306)
 12. Shi YW, Min FL, Zhou D, et al.: HLA-A*24:02 as a common risk factor for antiepileptic drug-induced cutaneous adverse reactions. *Neurology*. 2017, 88:2183-91. [10.1212/WNL.0000000000004008](https://doi.org/10.1212/WNL.0000000000004008)
 13. Ozeki T, Mushiroda T, Yowang A, et al.: Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. *Hum Mol Genet*. 2011, 20:1034-41. [10.1093/hmg/ddq537](https://doi.org/10.1093/hmg/ddq537)
 14. Manuyakorn W, Siripool K, Kamchaisatian W, et al.: Phenobarbital-induced severe cutaneous adverse drug reactions are associated with CYP2C19*2 in Thai children. *Pediatr Allergy Immunol*. 2013, 24:299-303. [10.1111/pai.12058](https://doi.org/10.1111/pai.12058)
 15. Ko TM, Chung WH, Wei CY, et al.: Shared and restricted T-cell receptor use is crucial for carbamazepine-induced Stevens-Johnson syndrome. *J Allergy Clin Immunol*. 2011, 128:1266-76.e11. [10.1016/j.jaci.2011.08.013](https://doi.org/10.1016/j.jaci.2011.08.013)
 16. Chung WH, Hung SI, Yang JY, et al.: Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Nat Med*. 2008, 14:1343-50. [10.1038/nm.1884](https://doi.org/10.1038/nm.1884)
 17. Su SC, Mockenhaupt M, Wolkenstein P, et al.: Interleukin-15 is associated with severity and mortality in Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Invest Dermatol*. 2017, 137:1065-73. [10.1016/j.jid.2016.11.034](https://doi.org/10.1016/j.jid.2016.11.034)
 18. Saito N, Qiao H, Yanagi T, et al.: An annexin A1-FPR1 interaction contributes to necroptosis of keratinocytes in severe cutaneous adverse drug reactions. *Sci Transl Med*. 2014, 6:245ra95. [10.1126/scitranslmed.3008227](https://doi.org/10.1126/scitranslmed.3008227)
 19. Letko E, Papaliodis DN, Papaliodis GN, Daoud YJ, Ahmed AR, Foster CS: Stevens-Johnson syndrome and toxic epidermal necrolysis: a review of the literature. *Ann Allergy Asthma Immunol*. 2005, 4:419-36. [10.1016/S1081-1206\(10\)61112-X](https://doi.org/10.1016/S1081-1206(10)61112-X)
 20. Jordan MH, Lewis MS, Jeng JG, Rees JM: Treatment of toxic epidermal necrolysis by burn units: another market or another threat?. *J Burn Care Rehabil*. 1991, 12:579-81. [10.1097/00004630-199110000-00015](https://doi.org/10.1097/00004630-199110000-00015)
 21. Shanbhag SS, Chodosh J, Fathy C, Goverman J, Mitchell C, Saeed HN: Multidisciplinary care in Stevens-Johnson syndrome. *Ther Adv Chronic Dis*. 2020, 11: [10.1177/2040622319894469](https://doi.org/10.1177/2040622319894469)
 22. Su JR, Haber P, Ng CS, Marquez PL, Dores GM, Perez-Vilar S, Cano MV: Erythema multiforme, Stevens Johnson syndrome, and toxic epidermal necrolysis reported after vaccination, 1999-2017. *Vaccine*. 2020, 38:1746-52. [10.1016/j.vaccine.2019.12.028](https://doi.org/10.1016/j.vaccine.2019.12.028)
 23. Oakley AM, Krishnamurthy K: Stevens-Johnson Syndrome. StatPearls Publishing, Treasure Island, FL; 2022.
 24. Mockenhaupt M, Viboud C, Dunant A, et al.: Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. *J Invest Dermatol*. 2008, 128:35-44. [10.1038/sj.jid.5701035](https://doi.org/10.1038/sj.jid.5701035)
 25. Roujeau JC, Kelly JP, Naldi L, et al.: Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med*. 1995, 333:1600-7. [10.1056/NEJM199512143332404](https://doi.org/10.1056/NEJM199512143332404)
 26. Arca E, Köse O, Erbil AH, Nişanci M, Akar A, Gür AR: A 2-year-old girl with Stevens-Johnson syndrome/toxic epidermal necrolysis treated with intravenous immunoglobulin. *Pediatr Dermatol*. 2005, 22:317-20. [10.1111/j.1525-1470.2005.22407.x](https://doi.org/10.1111/j.1525-1470.2005.22407.x)
 27. Cravens MG, Sherman N, Sawaya J: Ciprofloxacin-induced Stevens-Johnson syndrome with grapefruit juice consumption: a case report. *Cureus*. 2019, 11:e3827. [10.7759/cureus.3827](https://doi.org/10.7759/cureus.3827)
 28. Hällgren J, Tengvall-Linder M, Persson M, Wahlgren CF: Stevens-Johnson syndrome associated with ciprofloxacin: a review of adverse cutaneous events reported in Sweden as associated with this drug. *J Am Acad Dermatol*. 2003, 49:S267-9. [10.1016/s0190-9622\(03\)00478-x](https://doi.org/10.1016/s0190-9622(03)00478-x)
 29. Aversano MG, Schroeder J, Citterio A, et al.: Levofloxacin induced Stevens-Johnson syndrome/toxic epidermal necrolysis overlap syndrome: case reports. *Clin Transl Allergy*. 2014, 4:P91. [10.1186/2045-7022-4-S3-P91](https://doi.org/10.1186/2045-7022-4-S3-P91)
 30. Maciejewska J, Jankowski M, Zegarska B, Czajkowski R: Stevens-Johnson syndrome/toxic epidermal necrolysis presumably induced by norfloxacin. *Postepy Dermatol Alergol*. 2014, 31:194-6. [10.5114/pdia.2014.40796](https://doi.org/10.5114/pdia.2014.40796)
 31. Smelik M: Stevens-Johnson syndrome: a case study. *Perm J*. 2002, 6:29-31. [10.7812/TPP/02.997](https://doi.org/10.7812/TPP/02.997)
 32. Lau B, Mutyala D, Dhaliwal D: A case report of doxycycline-induced Stevens-Johnson syndrome. *Cornea*. 2011, 30:595-7. [10.1097/ICO.0b013e3181f05773](https://doi.org/10.1097/ICO.0b013e3181f05773)
 33. Yoon J, Lee SH, Kim TH, Choi DJ, Kim JP, Yoon TJ: Concurrence of Stevens-Johnson syndrome and bilateral parotitis after minocycline therapy. *Case Rep Dermatol*. 2010, 2:88-94. [10.1159/000314952](https://doi.org/10.1159/000314952)
 34. Nappe TM, Goren-Garcia SL, Jacoby JL: Stevens-Johnson syndrome after treatment with azithromycin: an uncommon culprit. *Am J Emerg Med*. 2016, 34:676.e1-3. [10.1016/j.ajem.2015.06.039](https://doi.org/10.1016/j.ajem.2015.06.039)
 35. Liccioli G, Mori F, Parronchi P, et al.: Aetiopathogenesis of severe cutaneous adverse reactions (SCARs) in children: a 9-year experience in a tertiary care paediatric hospital setting. *Clin Exp Allergy*. 2020, 50:61-73. [10.1111/cea.13513](https://doi.org/10.1111/cea.13513)
 36. Khaldi N, Miras A, Gromb S: Toxic epidermal necrolysis and clarithromycin. *Can J Clin Pharmacol*. 2005, 12:e264-8.
 37. Pejčić AV: Stevens-Johnson syndrome and toxic epidermal necrolysis associated with the use of macrolide antibiotics: a review of published cases. *Int J Dermatol*. 2021, 60:12-24. [10.1111/ijd.15144](https://doi.org/10.1111/ijd.15144)
 38. Mavilia L, Trifirò C, Mercuri SR: Stevens-Johnson syndrome caused by cefepime?. *J Pharmacol Pharmacother*. 2015, 6:35-6. [10.4103/0976-500X.149143](https://doi.org/10.4103/0976-500X.149143)
 39. Liberopoulos EN, Liamis GL, Elisaf MS: Possible cefotaxime-induced Stevens-Johnson syndrome. *Ann Pharmacother*. 2003, 37:812-4. [10.1345/aph.1C453](https://doi.org/10.1345/aph.1C453)
 40. Saavedra C, Cárdenas P, Castellanos H, Contreras K, Castro JR: Cephazolin-induced toxic epidermal necrolysis treated with intravenous immunoglobulin and N-acetylcysteine. *Case Reports Immunol*. 2012,

- 2012;931528. [10.1155/2012/931528](https://doi.org/10.1155/2012/931528)
41. Mazumdar G, Shome K: Stevens-Johnson syndrome following use of metronidazole in a dental patient . *Indian J Pharmacol*. 2014, 46:121-2. [10.4103/0253-7613.125193](https://doi.org/10.4103/0253-7613.125193)
 42. Pitche P, Mouzou T, Padonou C, Tchangai-Walla K: Stevens-Johnson syndrome and toxic epidermal necrolysis after intake of rifampicin-isoniazid: report of 8 cases in HIV-infected patients in Togo. (Article in French). *Med Trop (Mars)*. 2005, 65:359-62.
 43. Sahagún Flores JE, Soto Ortiz JA, Tovar Méndez CE, Cárdenas Ochoa EC, Hernández Flores G: Stevens-Johnson syndrome plus intrahepatic cholestasis caused by clindamycin or chlorpheniramine. (Article in Spanish). *Dermatol Online J*. 2009, 15:12.
 44. Alexander II, Greenberger PA: Vancomycin-induced Stevens-Johnson syndrome. *Allergy Asthma Proc*. 1996, 17:75-8. [10.2500/108854196778645029](https://doi.org/10.2500/108854196778645029)
 45. Lipový B, Říhová H, Wilková M, Hanslianová M, Kyclová J, Brychta P: The first case of nitrofurantoin-induced toxic epidermal necrolysis?. *Dermatol Pract*. 2016, 10:197-200. [10.36290/der.2016.044](https://doi.org/10.36290/der.2016.044)
 46. Chen P, Lin JJ, Lu CS, et al.: Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan . *N Engl J Med*. 2011, 364:1126-33. [10.1056/NEJMoa1009717](https://doi.org/10.1056/NEJMoa1009717)
 47. Lin LC, Lai PC, Yang SF, Yang RC: Oxcarbazepine-induced Stevens-Johnson syndrome: a case report . *Kaohsiung J Med Sci*. 2009, 25:82-6. [10.1016/S1607-551X\(09\)70045-2](https://doi.org/10.1016/S1607-551X(09)70045-2)
 48. Kodliwadmth A: Phenytoin-induced Stevens-Johnson syndrome with myocarditis: a rare case report . *Int Med Case Rep J*. 2017, 10:229-31. [10.2147/IMCRJ.S135643](https://doi.org/10.2147/IMCRJ.S135643)
 49. Pirau L, Lui F: A case report on lamotrigine complications and review of the literature . *J Hosp Med Manage*. 2018, 4:9. [10.4172/2471-9781.100046](https://doi.org/10.4172/2471-9781.100046)
 50. Hilas O, Charneski L: Lamotrigine-induced Stevens-Johnson syndrome. *Am J Health Syst Pharm*. 2007, 64:273-5. [10.2146/ajhp060071](https://doi.org/10.2146/ajhp060071)
 51. Gaur S, Agnihotri R: Phenobarbital induced Stevens-Johnson syndrome in a child . *Indian J Pharmacol*. 2012, 44:531-2. [10.4103/0253-7613.99344](https://doi.org/10.4103/0253-7613.99344)
 52. Naveen K, Arunkumar J, Hanumanthayya K, Pai V: Stevens-Johnson syndrome induced by sodium valproate monotherapy. *Int J Crit Illn Inj Sci*. 2012, 2:44-5. [10.4103/2229-5151.94904](https://doi.org/10.4103/2229-5151.94904)
 53. Zou LP, Ding CH, Song ZJ, Li XF: Stevens-Johnson syndrome induced by levetiracetam . *Seizure*. 2012, 21:823-5. [10.1016/j.seizure.2012.09.005](https://doi.org/10.1016/j.seizure.2012.09.005)
 54. Borrelli EP, Lee EY, Descoteaux AM, Kogut SJ, Caffrey AR: Stevens-Johnson syndrome and toxic epidermal necrolysis with antiepileptic drugs: an analysis of the US Food and Drug Administration Adverse Event Reporting System. *Epilepsia*. 2018, 59:2318-24. [10.1111/epi.14591](https://doi.org/10.1111/epi.14591)
 55. Noguchi Y, Takaoka M, Hayashi T, Tachi T, Teramachi H: Antiepileptic combination therapy with Stevens-Johnson syndrome and toxic epidermal necrolysis: analysis of a Japanese pharmacovigilance database. *Epilepsia*. 2020, 61:1979-89. [10.1111/epi.16626](https://doi.org/10.1111/epi.16626)
 56. Tetrazepam-containing medicines. (2018). Accessed: December 14, 2022: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Tetrazepam_containing_medicinal_products/...
 57. Jawaro T, Kumar A, Pistun O, Dixit D: Stevens-Johnson syndrome associated with chlordiazepoxide . *J Pharm Technol*. 2018, 34:82-5. [10.1177/8755122517753595](https://doi.org/10.1177/8755122517753595)
 58. FDA drug safety communication: FDA warns of serious skin reactions with the anti-seizure drug Onfi (clobazam) and has approved label changes. (2017). Accessed: December 15, 2022: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-serious-skin-reactions...>
 59. Loncar C, Franić T, Bilusić M: Toxic epidermal necrolysis caused by flurazepam?. *Psychiatr Danub*. 2005, 17:236-9.
 60. PubChem compound summary for CID 2717, chlormezanone . (2004). Accessed: March 8, 2023: <https://pubchem.ncbi.nlm.nih.gov/compound/Chlormezanone>.
 61. Ouni B, Fathallah N, Ben-Sayed N, Abdessayed N, Slim R, Sriha B, Ben Salem C: Fatal toxic epidermal necrolysis probably related to glimepiride in a patient with a medical history of hypersensitivity to sulfamethoxazole-trimethoprim. *Br J Clin Pharmacol*. 2021, 87:1591-3. [10.1111/bcp.14499](https://doi.org/10.1111/bcp.14499)
 62. Cheng JB, Anderson RC, Cruz PD Jr: Stevens-Johnson syndrome associated with glipizide therapy . *Dermatitis*. 2006, 17:36-8. [10.2310/6620.2006.05038](https://doi.org/10.2310/6620.2006.05038)
 63. Kumar P, Chauhan A, Charaniya R, Ghosh A, Tandon V: Metolazone associated Stevens Johnson syndrome-toxic epidermal necrolysis overlap. *J Clin Diagn Res*. 2016, 10:FD01-2. [10.7860/JCDR/2016/17768.7404](https://doi.org/10.7860/JCDR/2016/17768.7404)
 64. Stevens Johnson syndrome linked to aldactone blood pressure drug . (2015). Accessed: December 2, 2022: <https://topclassactions.com/lawsuit-settlements/lawsuit-news/aldactone-a-prescription-blood-pressure-drug-has-recentl....>
 65. Wright AA, Vesta KS, Stark JE, Smith WJ: Stevens-Johnson syndrome associated with furosemide: a case report. *J Pharm Pract*. 2010, 23:367-70. [10.1177/0897190010362260](https://doi.org/10.1177/0897190010362260)
 66. Demadex. (2023). Accessed: March 8, 2023: <https://www.rxlist.com/demadex-side-effects-drug-center.htm>.
 67. Reddy S, Aron BK, Stewart J: A life-threatening case of torsemide-induced toxic epidermal necrolysis associated with the treatment of anasarca. *Cureus*. 2022, 14:e22895. [10.7759/cureus.22895](https://doi.org/10.7759/cureus.22895)
 68. Shirato S, Kagaya F, Suzuki Y, Joukou S: Stevens-Johnson syndrome induced by methazolamide treatment . *Arch Ophthalmol*. 1997, 115:550-3. [10.1001/archophth.1997.01100150552021](https://doi.org/10.1001/archophth.1997.01100150552021)
 69. Chun JS, Yun SJ, Lee JB, Kim SJ, Won YH, Lee SC: Toxic epidermal necrolysis induced by the topical carbonic anhydrase inhibitors brinzolamide and dorzolamide. *Ann Dermatol*. 2008, 20:260-2. [10.5021/ad.2008.20.4.260](https://doi.org/10.5021/ad.2008.20.4.260)
 70. Shao QH, Yin XD, Zeng N, et al.: Stevens-Johnson syndrome following non-steroidal anti-inflammatory drugs: a real-world analysis of post-marketing surveillance data. *Front Pediatr*. 2022, 10:896867. [10.3389/fped.2022.896867](https://doi.org/10.3389/fped.2022.896867)
 71. Sateesh KSK, Kumar SDS, Raghavendra NCV, Kumar KS: A case report on diclofenac induced Stevens Johnson syndrome. *J Basic Clinic Pharm*. 2018, 9:109-10.
 72. Gui MZ, Ni M, Yin XD, Zhang T, Li ZL: Ibuprofen induced Stevens-Johnson syndrome and liver injury in

- children: a case report. *Transl Pediatr.* 2021, 10:1737-42. [10.21037/tp-21-8](#)
73. Nakamura R, Ochi F, Chisaka T, Jogamoto T, Eguchi M: Acetaminophen-induced Stevens-Johnson syndrome with lethal lung injury: a case report. *Clin Case Rep.* 2022, 10:e6294. [10.1002/ccr3.6294](#)
 74. Milosavljević MN, Pejčić AV, Milosavljević JZ: A review of published cases of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with the use of acetaminophen. *Cutan Ocul Toxicol.* 2021, 40:280-92. [10.1080/15569527.2021.1942896](#)
 75. Jan V, Toledano C, Machet L, Machet MC, Vaillant L, Lorette G: Stevens-Johnson syndrome after sertraline. *Acta Derm Venereol.* 1999, 79:401. [10.1080/000155599750010472](#)
 76. Agrawal R, Almoghrabi A, Attar BM, Gandhi S: Fluoxetine-induced Stevens-Johnson syndrome and liver injury. *J Clin Pharm Ther.* 2019, 44:115-8. [10.1111/jcpt.12760](#)
 77. Soni A, Mane A: Fluoxetine-induced liver injury and skin reaction: a case report. *Indian J Psychiatry.* 2021, 63:405-6. [10.4103/psychiatry.IndianJPsychiatry.320_20](#)
 78. Strawn JR, Whitsel R, Nandagopal JJ, Delbello MP: Atypical Stevens-Johnson syndrome in an adolescent treated with duloxetine. *J Child Adolesc Psychopharmacol.* 2011, 21:91-2. [10.1089/cap.2010.0071](#)
 79. Cymbalta caused Stevens Johnson syndrome, lawsuit says. (2014). Accessed: December 20, 2022: <https://topclassactions.com/lawsuit-settlements/lawsuit-news/cymbalta-caused-stevens-johnson-syndrome-lawsuit-says/>.
 80. Bhasin A, Gurtoo A, Gupta L, Aggarwal G: First case of mirtazepine-induced Stevens-Johnson syndrome from India. *Indian J Pharmacol.* 2012, 44:656-8. [10.4103/0253-7613.100411](#)
 81. Wang F, Ma Z, Wu X, Liu L: Allopurinol-induced toxic epidermal necrolysis featuring almost 60% skin detachment. *Medicine (Baltimore).* 2019, 98:e16078. [10.1097/MD.00000000000016078](#)
 82. Cocca S, Viviano M: Stevens-Johnson syndrome and abuse of anabolic steroids. *J Korean Assoc Oral Maxillofac Surg.* 2017, 43:57-60. [10.5125/jkaoms.2017.43.1.57](#)
 83. Koh WL, Tay YK, Koh MJ: Danazol-induced Stevens-Johnson syndrome in a patient with systemic lupus erythematosus. *Dermatol Online J.* 2015, 21:
 84. Jarrett B, Ghazala S, Chao J, Chaudhary S: Case of Steven-Johnson syndrome in a male with breast cancer secondary to docetaxel/cyclophosphamide therapy. *BMJ Case Rep.* 2016, 2016: [10.1136/bcr-2016-217255](#)
 85. Minakawa S, Matsuzaki Y, Nakajima K, et al.: Tegafur/gimeracil/oteracil (TS-1) induced Stevens-Johnson syndrome: case report. *Dermatol Sin.* 2013, 31:154-6. [10.1016/j.dsi.2012.12.005](#)
 86. Wang K, Gu C, Hu D: Stevens-Johnson syndrome associated with TS-1 in a patient with gastric cancer: a case report. *Br J Clin Pharmacol.* 2021, 87:1554-60. [10.1111/bcp.14493](#)
 87. Kubicki SL, Welborn ME, Patel AB: Toxic epidermal necrolysis during cotherapy with ipilimumab and nivolumab. *J Immunother Precis Oncol.* 2020, 1:78-81. [10.4103/JIPO.JIPO.7_18](#)
 88. Coleman E, Ko C, Dai F, Tomayko MM, Kluger H, Leventhal JS: Inflammatory eruptions associated with immune checkpoint inhibitor therapy: a single-institution retrospective analysis with stratification of reactions by toxicity and implications for management. *J Am Acad Dermatol.* 2019, 80:990-7. [10.1016/j.jaad.2018.10.062](#)
 89. Hiraki A, Aoe K, Murakami T, Maeda T, Eda R, Takeyama H: Stevens-Johnson syndrome induced by paclitaxel in a patient with squamous cell carcinoma of the lung: a case report. *Anticancer Res.* 2004, 24:1135-7.
 90. Diab O, Mcentire D, Kassim T, et al.: Docetaxel-induced Stevens-Johnson syndrome in a patient with metastatic prostate adenocarcinoma. *Case Rep Oncol Med.* 2019, 2019:7928752. [10.1155/2019/7928752](#)
 91. Deng M, Chai H, Yang M, et al.: Stevens-Johnson syndrome caused by enzalutamide: a case report and literature review. *Front Oncol.* 2021, 11:736975. [10.3389/fonc.2021.736975](#)
 92. Israr S, Mellon CR, Springs HJ, Quan A, Matthews M: Enzalutamide associated with Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) overlap: a case report. *Surg Sci.* 2021, 12:421-6. [10.4236/ss.2021.1212045](#)
 93. Madabhavi I, Revannasiddaiah S, Patel A, Anand A: Toxic epidermal necrolysis with the use of tamoxifen. *BMJ Case Rep.* 2015, 2015: [10.1136/bcr-2014-209102](#)
 94. Chen CB, Wu MY, Ng CY, et al.: Severe cutaneous adverse reactions induced by targeted anticancer therapies and immunotherapies. *Cancer Manag Res.* 2018, 10:1259-73. [10.2147/CMAR.S163391](#)
 95. Kowalczyk A, Radecka B: Stevens-Johnson syndrome in breast cancer patient treated with ribociclib. *Oncol Clin Pract.* 2022, 19:59-62. [10.5603/ocp.2022.0004](#)
 96. Maloney NJ, Ravi V, Cheng K, Bach DQ, Worswick S: Stevens-Johnson syndrome and toxic epidermal necrolysis-like reactions to checkpoint inhibitors: a systematic review. *Int J Dermatol.* 2020, 59:e183-8. [10.1111/ijd.14811](#)
 97. Ng CY, Chen CB, Wu MY, et al.: Anticancer drugs induced severe adverse cutaneous drug reactions: an updated review on the risks associated with anticancer targeted therapy or immunotherapies. *J Immunol Res.* 2018, 2018:5376476. [10.1155/2018/5376476](#)
 98. Das A, Sil A, Mishra V, Das NK: Steven's Johnson syndrome with toxic epidermal necrolysis due to thalidomide in a case of multiple myeloma. *Indian J Pharmacol.* 2014, 46:557-9. [10.4103/0253-7613.140598](#)
 99. Allegra A, Alonci A, Penna G, et al.: Stevens-Johnson syndrome after lenalidomide therapy for multiple myeloma: a case report and a review of treatment options. *Hematol Oncol.* 2012, 30:41-5. [10.1002/hon.1000](#)
 100. Matsushita K, Ozaki A, Inoue H, et al.: Stevens-Johnson syndrome induced by mizoribine in a patient with systemic lupus erythematosus. *Mod Rheumatol.* 2006, 16:113-6. [10.3109/s10165-006-0467-5](#)
 101. Sueki H, Kitami Y, Watanabe H: Severe cutaneous adverse reactions during tapering of high-dose systemic steroid therapy for autoimmune diseases: implications for non-HIV immune reconstitution inflammatory syndrome. *Case Rep Dermatol.* 2019, 11:166-74. [10.1159/000500945](#)
 102. Arora R, Pande RK, Panwar S, Gupta V: Drug-related Stevens-Johnson syndrome and toxic epidermal necrolysis: a review. *Indian J Crit Care Med.* 2021, 25:575-9. [10.5005/jp-journals-10071-23826](#)
 103. Aroke D, Tchouakam DN, Awungia AT, Mapoh SY, Ngassa SN, Kadia BM: Ivermectin induced Steven-Johnsons syndrome: case report. *BMC Res Notes.* 2017, 10:179. [10.1186/s13104-017-2500-5](#)
 104. Zuo W, Wen LP, Li J, Mei D, Fu Q, Zhang B: Oseltamivir induced Stevens-Johnson syndrome/toxic epidermal necrolysis-case report. *Medicine (Baltimore).* 2019, 98:e15553. [10.1097/MD.00000000000015553](#)

105. Chattopadhyay P, Sarma N: Adefovir-induced Stevens-Johnson syndrome and toxic epidermal necrolysis overlap syndrome. *Singapore Med J*. 2011, 52:e31-4.
106. Xavier S, Athira P, Mathew AC, Basheer H, Rahana K, Pk MH, Chandrasekhar D: Tenofovir-induced Stevens-Johnson syndrome in a patient with acute hepatitis B: a rare case report. *J Am Pharm Assoc* (2003). 2020, 60:e365-9. [10.1016/j.japh.2020.06.029](https://doi.org/10.1016/j.japh.2020.06.029)
107. Singh H, Kachhap VK, Kumar BN, Nayak K: Nevirapine induced Stevens-Johnson syndrome in an HIV infected patient. *Indian J Pharmacol*. 2011, 43:84-6. [10.4103/0253-7613.75680](https://doi.org/10.4103/0253-7613.75680)
108. Saka B, Akakpo AS, Bassowa A, et al.: Non-nucleoside reverse transcriptase inhibitors (NNRTIs)-induced Stevens-Johnson syndrome and gynecomastia in an HIV-infected child: a case report. *Ann Dermatol Venereol*. 2018, 145:773-6. [10.1016/j.annder.2018.07.022](https://doi.org/10.1016/j.annder.2018.07.022)
109. Paik S, Pal A, Sen S, Pramanick N, Tripathi SK: A suspected case of efavirenz-induced Stevens-Johnson syndrome. *Drug Saf Case Rep*. 2015, 2:15. [10.1007/s40800-015-0019-z](https://doi.org/10.1007/s40800-015-0019-z)
110. Sen SS, Sil A, Chakraborty U, Chandra A: Stevens-Johnson syndrome-toxic epidermal necrolysis: a fatal cutaneous adverse reaction to oral acyclovir. *BMJ Case Rep*. 2020, 13:e238555. [10.1136/bcr-2020-238555](https://doi.org/10.1136/bcr-2020-238555)
111. Banik B, Bhar D, Sil A: Terbinafine-induced Steven-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) overlap. *Postgrad Med J*. 2021, 97:630-1. [10.1136/postgradmedj-2020-138326](https://doi.org/10.1136/postgradmedj-2020-138326)
112. Jao T, Tsai TH, Jeng JS: Aggrenox (Asasantin Retard)-induced Stevens-Johnson syndrome. *Br J Clin Pharmacol*. 2009, 67:264-5. [10.1111/j.1365-2125.2008.03340.x](https://doi.org/10.1111/j.1365-2125.2008.03340.x)
113. Teo SL, Santosa A, Bigliardi PL: Stevens-Johnson syndrome/toxic epidermal necrolysis overlap induced by fexofenadine. *J Investig Allergol Clin Immunol*. 2017, 27:191-3. [10.18176/jiaci.0158](https://doi.org/10.18176/jiaci.0158)
114. Oskay T, Özçelik T, Kutluay L: Stevens-Johnson syndrome associated with ramipril. *Int J Dermatol*. 2003, 42:580-1. [10.1046/j.1365-4362.2003.01838.x](https://doi.org/10.1046/j.1365-4362.2003.01838.x)
115. Bonnici H, Bygum A: Losartan-induced Stevens-Johnson syndrome in a geriatric patient. (Article in Danish) . *Ugeskr Laeger*. 2007, 169:1233-4.
116. Frey N, Bodmer M, Bircher A, Jick SS, Meier CR, Spoendlin J: Stevens-Johnson syndrome and toxic epidermal necrolysis in association with commonly prescribed drugs in outpatient care other than anti-epileptic drugs and antibiotics: a population-based case-control study. *Drug Saf*. 2019, 42:55-66. [10.1007/s40264-018-0711-x](https://doi.org/10.1007/s40264-018-0711-x)
117. Mukherjee S, Saha D, Dasgupta S, Tripathi SK: Case report: suspected case of Stevens-Johnson syndrome and toxic epidermal necrolysis overlap due to ursodeoxycholic acid. *EMJ Dermatol*. 2020, 8:96-9. [10.33590/emjdermatol/20-00117](https://doi.org/10.33590/emjdermatol/20-00117)
118. Yang CY, Chen CH, Wang HY, Hsiao HL, Hsiao YH, Chung WH: Strontium ranelate related Stevens-Johnson syndrome: a case report. *Osteoporos Int*. 2014, 25:1813-6. [10.1007/s00198-014-2688-3](https://doi.org/10.1007/s00198-014-2688-3)
119. Carrera D, Ulloa JG: Iodinated contrast-induced Stevens-Johnson syndrome: a report of a rare complication for a common imaging agent. *J Vasc Surg Cases Innov Tech*. 2022, 8:455-7. [10.1016/j.jvscit.2022.06.015](https://doi.org/10.1016/j.jvscit.2022.06.015)
120. Laffitte E, Nenadov Beck M, Hofer M, Hohl D, Panizzon RG: Severe Stevens-Johnson syndrome induced by contrast medium iopentol (Imagopaque). *Br J Dermatol*. 2004, 150:376-8. [10.1111/j.1365-2133.2003.05763.x](https://doi.org/10.1111/j.1365-2133.2003.05763.x)
121. Lim JH, Kim HS, Kim HO, Park YM: Stevens-Johnson syndrome following occupational exposure to carbamate insecticide. *J Dermatol*. 2010, 37:182-4. [10.1111/j.1346-8138.2009.00784.x](https://doi.org/10.1111/j.1346-8138.2009.00784.x)
122. Roujeau JC: Immune mechanisms in drug allergy. *Allergol Int*. 2006, 55:27-33. [10.2332/allergolint.55.27](https://doi.org/10.2332/allergolint.55.27)
123. Rzany B, Hering O, Mockenhaupt M, Schröder W, Goerttler E, Ring J, Schöpf E: Histopathological and epidemiological characteristics of patients with erythema exudativum multiforme major, Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol*. 1996, 135:6-11.
124. Gronich N, Maman D, Stein N, Saliba W: Culprit medications and risk factors associated with Stevens-Johnson syndrome and toxic epidermal necrolysis: population-based nested case-control study. *Am J Clin Dermatol*. 2022, 23:257-66. [10.1007/s40257-021-00661-0](https://doi.org/10.1007/s40257-021-00661-0)
125. Hasegawa A, Abe R: Recent advances in managing and understanding Stevens-Johnson syndrome and toxic epidermal necrolysis. *F1000Res*. 2020, 9:[10.12688/f1000research.24748.1](https://doi.org/10.12688/f1000research.24748.1)
126. Liotti L, Caimmi S, Bottau P, et al.: Clinical features, outcomes and treatment in children with drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis. *Acta Biomed*. 2019, 90:52-60. [10.23750/abm.v90i3-S.8165](https://doi.org/10.23750/abm.v90i3-S.8165)
127. Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC: Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death?. *Arch Dermatol*. 2000, 136:323-7. [10.1001/archderm.136.3.323](https://doi.org/10.1001/archderm.136.3.323)
128. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P: SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol*. 2000, 115:149-53. [10.1046/j.1523-1747.2000.00061.x](https://doi.org/10.1046/j.1523-1747.2000.00061.x)
129. Dorafshar AH, Dickie SR, Cohn AB, Aycock JK, O'Connor A, Tung A, Gottlieb LJ: Antishear therapy for toxic epidermal necrolysis: an alternative treatment approach. *Plast Reconstr Surg*. 2008, 122:154-60. [10.1097/PRS.0b013e3181773d5d](https://doi.org/10.1097/PRS.0b013e3181773d5d)