The Journal of Dermatology

GUIDELINES

Guidelines for the Management of Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis 2025 Supplement

Hideaki Watanabe[1,2] | Youichi Ogawa[3] | Yukie Yamaguchi[4] | Saeko Nakajima[5] | Yoshiko Mizukawa[6] | Taisei Mushiroda[7] | Hayato Takahashi[8] | Toshiharu Fujiyama[9] | Chie Sotozono[10] | Yoshiko Kaneko[11] | Akito Hasegawa[12] | Kae Kobayashi[2] | Yuma Sunaga[2] | Yuko Watanabe[4] | Takashi Nomura[5] | Kenji Kabashima[5] | Ayano Inui[13] | Mikiya Fujieda[14] | Mayumi Ueta[10] | Natsumi Hama[12] | Mikiko Tohyama[15] | Riichiro Abe[12]

[1]Department of Dermatology, Showa Medical University Northern Yokohama Hospital, Yokohama, Japan | [2]Department of Dermatology, Showa Medical University School of Medicine, Tokyo, Japan | [3]Department of Dermatology, Faculty of Medicine, University of Yamanashi, Yamanashi, Japan | [4]Department of Environmental Immuno- Dermatology, Graduate School of Medicine, Yokohama City University, Yokohama, Japan | [5]Department of Dermatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan | [6]Department of Dermatology, Kyorin University, Tokyo, Japan | [7]Laboratory for Pharmacogenomics, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan | [8]Department of Dermatology, School of Medicine, Keio University, Tokyo, Japan | [9]Department of Dermatology, Hamamatsu University School of Medicine, Hamamatsu, Japan | [10]Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan | [11]Department of Pulmonary Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan | [12]Division of Dermatology, Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Japan | [13]Department of Pediatric Hepatology and Gastroenterology, Saiseikai Yokohamashi Tobu Hospital, Yokohama, Japan | [14]Department of Pediatrics, Kochi Medical School, Kochi University, Kochi, Japan | [15]Department of Dermatology, NHO Shikoku Cancer Center, Matsuyama, Japan

Correspondence: Hideaki Watanabe (hwatanabe@med.showa-u.ac.jp) | Riichiro Abe (aberi@med.niigata-u.ac.jp)

Received: 30 November 2025 | **Revised:** 9 December 2025 | **Accepted:** 12 December 2025

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are characterized by high fever, body malaise, and multiple erythema, erosions, and blisters on the skin and mucocutaneous junction. They are considered life-threatening and intractable diseases that leave sequelae, including blindness and respiratory disorders. The diagnostic criteria for SJS/TEN were developed in 2005 by the Japanese Ministry of Health, Labour and Welfare Research Group on Severe Erythema Multiforme in Japan. To further understand the actual clinical scenario, the first epidemiological survey targeting dermatologists' full-time facilities nationwide was conducted from 2005 to 2007 and subsequently published. In 2015, the Japanese guidelines for the management of SJS and TEN were established. The second national survey for SJS/TEN, conducted from 2016 to 2018, identified vascular disease, malignancy, and diabetes mellitus as risk factors for SJS/TEN development. Moreover, they also identified sepsis and diabetes as risk factors for death and sepsis, respectively. In this survey, the mortality rates of both SJS and TEN were higher than those recorded in the first national survey.

Based on these results, we revised the existing guidelines by incorporating recent knowledge on the pathogenesis, medical complications, treatment, and prognosis prediction of SJS/TEN with the aim of saving the lives of patients with SJS/TEN in the future. This addendum provides standard guidelines at this point. However, several of these guidelines are based on the committee's opinions, because clinical studies with high-level evidence are limited due to the rarity of these diseases, and their pathogeneses are often unclear. In actual practice, the treatment approach must consider each patient's situation, and the guidelines are not intended to force treatment selection or limit a physician's discretion.

Levels of Evidence Classification:

I: Systematic review/meta-analysis.

II: One or more randomized controlled trials.

III: Nonrandomized controlled trials.

IVa: Epidemiological studies, such as cohort studies.

IVb: Epidemiological studies, such as case–control and cross-sectional studies.

V: Descriptive studies, including case reports and case series studies.

VI: Personal opinion.

1 | CQ1: What Immunological Mechanisms Underlie SJS/TEN?

Recommendation Statement: Keratinocyte death leads to the formation of blisters and erosions. The death of these cells is mediated via different types of regulated cell death processes, including apoptosis and necroptosis.

Explanation

The culprit drug is recognized as a foreign antigen in individuals with specific human leukocyte antigen (HLA) alleles. Subsequently, activated T cells and natural killer (NK) cells release soluble and cytotoxic molecules, resulting in the death of epidermal keratinocytes. Death of epidermal keratinocytes is mediated by different types of regulated cell death processes, such as apoptosis and necroptosis. Apoptosis is induced by soluble Fas ligand, perforin/granzyme B, and granulysin [1, 2] (Figure 1). Necroptosis is caused by annexin A1 released by monocytes [3]. Monocyte-derived annexin A1 binds to formyl peptide receptor 1 (FPR1), an annexin A1 receptor specifically expressed on SJS/TEN keratinocytes. The *de novo* FPR1 expression on keratinocytes is induced by an antimicrobial peptide LL-37 derived from neutrophil extracellular traps (NETs) released by activated skin-infiltrating neutrophils [4] (Figure 1).

Cytokines, including tumor necrosis factor-alpha (TNF-α), released by cytotoxic T cells and other immune cells also play an important role in inducing death of epidermal keratinocytes [5]. TNF-α not only induces apoptosis and necroptosis in epidermal keratinocytes but also upregulates granulysin mRNA expression in immune cells [6]. The other possible mechanisms underlying the death of epidermal keratinocytes include defective regulatory T-cell function due to concomitant infection and aberrant T-cell activation due to the enhanced production of pro-inflammatory cytokines.

2 | CQ2: Do Any Drugs Pose a High Risk of SJS/TEN?

Recommendation Statement: For SJS and TEN, the most commonly suspected high-risk drugs include antibiotics and antipyretic analgesics.

Explanation

In the second national survey of SJS/TEN, we analyzed 315 SJS and 174 TEN cases [7]. In our results, the suspected SJS-associated drugs were antibiotics (19.2%), antipyretic, analgesic, and anti-inflammatory drugs (8.1%), antiepileptic drugs (7.2%), gastrointestinal ulcer treatment drugs (6.9%), and cardiovascular disease treatment drugs (6.6%). The suspected TEN-associated drugs included antibiotics (30%); antipyretic, analgesic, and anti-inflammatory agents (13.5%), cardiovascular drugs (11%); gastrointestinal ulcer treatment drugs (6.7%); and anticancer agents (4.7%). The top three suspected drugs in this survey were the same as in the 2005–2007 survey, with antibiotics and antipyretic, analgesics, and anti-inflammatory drugs accounting for more than one-third of the overall drug-related risk of SJS/TEN [7].

Recently, there have been scattered reports of association of SJS/TEN with novel anticancer agents, molecularly targeted drugs, immune checkpoint inhibitors, and prostate cancer hormone therapy drugs. Given that these new drugs are expected to be increasingly used in clinical practice, dermatologists will need to acquire sufficient knowledge about them. Moreover, dermatologists must actively participate in treatment decisions involving other specialties, such as considering the continuation of treatment in light of an underlying disease.

3 | CQ3: Which Approaches are Used for the Identification of the Causative Drug of SJS/TEN in Japan?

Recommendation Statement: Among the existing diagnostic methods for SJS/TEN, patch tests, and drug-induced lymphocyte stimulation test (DLST, i.e., lymphocyte transformation

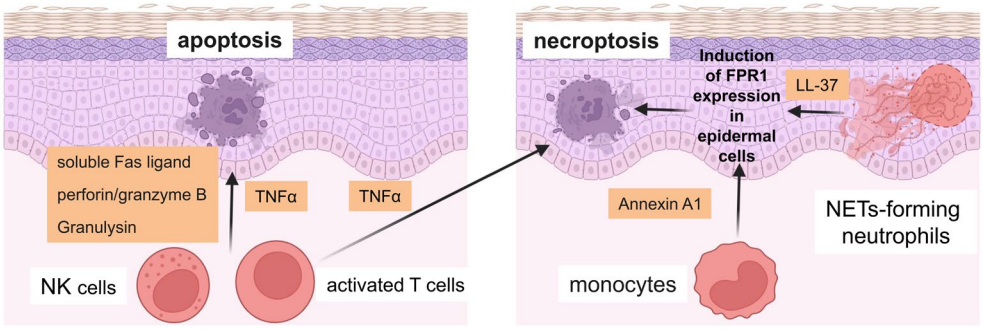

FIGURE 1 | The mechanism underlying epidermal cell death in Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Epidermal cell death is mediated by various mechanisms of cell death, including apoptosis and necroptosis. Apoptosis is induced by soluble Fas ligands, perforin/granzyme B, granulin, and other factors. Necroptosis is triggered by annexin A1 released by monocytes, and neutrophil-released neutrophil extracellular traps might be involved in necroptosis. Tumor necrosis factor (TNF)-α can directly induce both apoptosis and necroptosis.

TABLE 1 | Genes associated with the risk of developing SJS/TEN.

Causative drug	Related gene (alleles)	Populations	References
Carbamazepine	HLA-B[a] 15:02	Taiwanese, Chinese, Thai, Malays	[9–12]
	HLA-B[a] 15:11	Japanese	[13, 14]
Allopurinol	HLA-B[a] 58:01[a]	Taiwanese, Caucasian, Japanese	[15–17]
Cold medications	HLA-A[a] 02:06	Japanese	[18]
Phenobarbital	HLA-B[a] 51:01	Japanese	[19]
	CYP2C19[a] 2[b]	Thai	[20]
Zonisamide	HLA-A[a] 02:07	Japanese	[19]
Phenytoin	HLA-B[a] 15:02[b]	Taiwanese, Thai	[21]
	HLA-B[a] 51:01[b]	Taiwanese, Thai, Japanese	[21]
	HLA-B[a] 13:01[b]	Taiwanese, Thai	[21]
	CYP2C9[a] 3[b]	Taiwanese, Thai, Japanese, Malays	[21, 22]
Lamotrigine	HLA-B[a] 15:02	Chinese, Taiwanese, Thai	[23]
	HLA-A[a] 24:02[c]	Korean, Chinese	[23]
Sulfonamide	HLA-A[a] 11:01[b]	Japanese	[24, 25]
	HLA-B[a] 39:01[b]	Japanese	[25]
	HLA-B[a] 56:03[b]	Japanese	[25]

Note: HLA alleles associated with the risk of developing SJS/TEN have been reported in diverse populations in addition to those specific to Japanese population.
[a]Also associated with HSS (hypersensitivity syndrome).
[b]Also associated with DIHS (drug-induced hypersensitivity syndrome).
[c]Also associated with MPE (maculopapular erythema).

test, LTT) are relatively useful in identifying the causative drug and are routinely performed in clinical practice.

Explanation

The second national survey on SJS/TEN [7] helped elucidate the current status of causative drug identification for SJS/TEN in Japan. The patch tests were performed in 13.3% and 13.8% of SJS and TEN cases, with positive rates of 28.6% and 20.8%, respectively. Further breakdown of representative positive cases revealed that four and three cases of SJS arose due to the use of antibiotics and antipyretic, analgesic, and anti-inflammatory agents. In contrast, the use of antibiotics; anticoagulants; antihypertensive agents; expectorants; and antipyretic, analgesic, and anti-inflammatory agents each led to one TEN case [7].

DLST was performed in 67.3% and 66.1% of SJS and TEN cases, with positive rates of 50% and 51.3%, respectively. The use of antipyretic, analgesic, and anti-inflammatory agents, antibiotics, and antiepileptic drugs led to the emergence of 48, 18, and 14 SJS cases, respectively. In contrast, the use of antipyretic, analgesic, and anti-inflammatory agents, antibiotics, and psychiatric drugs led to the emergence of 29, ten, and 6, TEN cases, respectively. These findings indicated that the use of antibiotics and antipyretic, analgesic, and anti-inflammatory agents was more commonly associated with positive cases. Given that DLST was covered by health insurance in 2008 and has become more widely adopted, the implementation rates for patch test and DLST observed in the second survey were lower [8] and higher [7] than the rates observed in the first survey, respectively.

4 | CQ4: Is There a Genetic Predisposition to Developing SJS/TEN?

Recommendation Statement: Numerous HLA alleles have been reported to be associated with the drug-related risk of developing SJS/TEN.

Explanation

HLA alleles associated with the risk of developing SJS/TEN have been reported in diverse populations (Table 1) [9–25]. Genetic analyses of Japanese patients with SJS/TEN have identified several HLA alleles associated with the risk of developing SJS/TEN, including HLA-B*58:01 in the antigout drug allopurinol and *HLA-B**15:11, HLA-B*51:01, and *HLA-A**02:07 in the antiepileptic drugs carbamazepine, phenobarbital, and zonisamide, respectively [13, 14, 17, 19]. Another study reported an association between HLA-A*02:06 and the risk of developing SJS/TEN with ocular complications caused by cold medications [18]. Regarding genetic polymorphisms in drug-metabolizing enzymes that affect systemic drug concentrations, an international meta-analysis involving Taiwanese, Malaysian, and Japanese populations reported that the loss-of-function allele (*CYP2C9*3*) of the primary metabolizing enzyme CYP2C9 for

the antiepileptic drug phenytoin is associated with the risk of developing phenytoin-induced SJS/TEN [21, 22].

5 | CQ5: Are There Any Underlying Conditions That Increase the Risk of Developing SJS/TEN?

Recommendation Statement: Cardiovascular disease, malignant tumors, diabetes, autoimmune diseases, as well as *Mycoplasma* and human immunodeficiency virus (HIV) infections are risk factors for developing SJS/TEN. Sepsis is a risk factor for mortality in patients with SJS/TEN.

Explanation

In the second survey, the underlying conditions and mortality risk factors of 315 SJS patients and 174 TEN patients were analyzed [7, 26]. The most prevalent underlying condition in SJS patients was cardiovascular disease, followed by malignant tumors, autoimmune diseases, and *Mycoplasma* infection [7]. The most common underlying condition in TEN patients was cardiovascular disease, followed by malignant tumors, diabetes, and *Mycoplasma* infection.

Furthermore, the incidence of malignant tumors was higher among SJS/TEN patients than in the general Japanese population [26]. In Germany, the prevalence of systemic lupus erythematosus (SLE) is higher among SJS/TEN patients than in the general population [27]. However, data on the prevalence of SLE in Japanese patients with SJS/TEN remain limited. SLE patients might suffer from TEN-like acute cutaneous lupus erythematosus, which can clinically resemble SJS/TEN, underscoring the importance of careful differential diagnosis [27].

In the United States, the incidence rate of SJS/TEN is 100-fold higher among HIV-infected individuals than in noninfected individuals [28]. Factors suggested to contribute to the higher risk of onset of SJS/TEN in HIV-infected individuals included polypharmacy, immune dysregulation, and mixed infections.

6 | CQ6: Are There Any Risk Factors Associated With Mortality in SJS/TEN Patients?

Recommendation Statement: Sepsis is a risk factor associated with mortality in patients with SJS/TEN. The main risk factors for sepsis onset include diabetes and systemic conditions requiring intensive care unit-level management.

Explanation

In the second national survey, patients with SJS and TEN exhibited mortality rates of 4.1% and 29.9%, respectively [7]. The key risk factor for mortality in SJS/TEN patients was sepsis [7, 26]. The mortality rate was higher among SJS/TEN patients who developed sepsis during the 2016–2018 period compared to those who did not develop sepsis [7, 26]. These results were consistent with the findings from previous domestic and international studies [29, 30].

The main risk factors for sepsis included diabetes and systemic conditions requiring intensive care unit-level management [26]. Although not statistically significant, patients receiving systemic corticosteroids before the onset of SJS/TEN tended to exhibit a higher incidence of sepsis [26].

7 | CQ7: Is the Pathogenesis of SJS/TEN With Severe Ocular Complications Understood?

Recommendation Statement: Flu-like symptoms suggestive of microbial infections are often observed in SJS/TEN cases with severe ocular complications, and the administration of medications to treat these symptoms frequently triggers SJS/TEN onset.

Explanation

Regarding the pathogenesis of SJS/TEN induced by cold medications [31–33], the suppression of prostaglandin E2 (PGE_2) production has been suggested to inhibit the anti-inflammatory mechanism mediated by the PGE_2–EP_3 receptor [31]. In mouse models, PGE_2 has been shown to suppress skin and mucosal inflammation, including that on the ocular surface, via the EP_3 receptor [34, 35].

In the SJS/TEN patients with severe ocular complications, EP_3 protein expression is markedly downregulated in ocular surface tissues [36]. Furthermore, increased levels of certain plasma microRNAs (miRNAs) have been implicated in the dysregulation of innate immune responses [37, 38]. These findings suggested that the abnormalities in the innate immune response to microbial agents might play a role in the development of SJS/TEN with severe ocular complications [39].

8 | CQ8: Are There Any New Treatments for Chronic Eye Sequelae?

Recommendation Statement: Novel treatment options for chronic ocular sequelae in SJS/TEN include specially designed rigid contact lenses and cultured autologous oral mucosal epithelial transplantation. Both are currently covered by health insurance in Japan.

Explanation

In the acute phase of SJS/TEN, extensive sloughing of the ocular surface epithelium leads to the loss of corneal epithelium, eventually resulting in conjunctival epithelial overgrowth onto the cornea—a condition known as corneal epithelial stem cell deficiency. This condition causes visual impairment due to corneal opacity, irregular astigmatism, and ocular surface adhesions.

To address these complications, a limbal rigid contact lens (Suncon Kyoto-CS) was developed and is currently covered by health insurance in Japan for patients with ocular sequelae of SJS/TEN [40, 41]. This lens, available in 13.0- and 14.0-mm diameters, is worn during the day and removed at night. It fully covers the cornea, improving visual acuity in patients who do not achieve sufficient vision with conventional glasses or contact lenses. Additionally, it alleviates dry eye symptoms and gradually reduces ocular surface inflammation with continued use [42].

In severe cases with ocular sequelae, ocular surface adhesion might progress. In such cases, amniotic membrane transplantation has been attempted but with limited success. Recently, cultured autologous oral mucosal epithelial sheet transplantation (COMET) has shown promising potential in improving severe adhesions [43]. The COMET sheet (Sakuracy) was approved in 2022 and has been covered by health insurance in Japan since 2023.

COMET, followed by the use of a limbal rigid contact lens, can improve visual acuity, even in end-stage cases [44, 45]. This contact lens also helps maintain long-term ocular surface stability. In cases where corneal opacity complicates cataract surgery, combining COMET with cataract surgery facilitates the procedure and enhances visual outcomes.

9 | CQ9: Are There Any Factors Associated With the Worsening of Acute Ocular Mucosal Damage?

Recommendation Statement: In patients who develop SJS/TEN at a young age after receiving non-steroidal anti-inflammatory drugs (NSAIDs), ocular mucosal epithelial damage might worsen even after the treatment has been initiated.

Explanation

The presence of epithelial defects or pseudomembranes on the ocular surface during the acute phase of SJS/TEN indicates severe ocular involvement and is associated with a high risk of long-term ocular sequelae, including visual impairment and dry eye [32].

Ocular lesions tend to worsen when SJS/TEN is triggered by cold medications or NSAIDs [32]. Additionally, SJS/TEN onset at a younger age is associated with the development of more severe ocular complications [32]. Even with prompt commencement of treatment after diagnosis, the ocular complications might progress [46]. Therefore, in children and young adults who develop SJS/TEN following NSAID use, clinicians should be aware of the high risk of worsening ocular surface damage despite appropriate treatment.

10 | CQ10: Is Steroid Eye Drop Therapy Effective Against Acute-Phase Ocular Mucosal Damage?

Recommendation Statement: In cases with severe ocular involvement during the acute phase of SJS/TEN, high-dose topical steroid therapy should be administered alongside systemic corticosteroid pulse therapy, with close monitoring for potential infections.

Explanation

In cases of severe ocular involvement during the acute phase, such as epithelial defects or pseudomembranes, intensive ocular surface inflammation occurs on the ocular surface. In such cases, high-dose topical steroids should be administered in conjunction with systemic corticosteroid pulse therapy, with close monitoring for the development of potential infections [47, 48].

Ocular surface inflammation often persists longer than systemic inflammation; therefore, topical anti-inflammatory therapy should be tapered more gradually than systemic treatment.

In a case series involving ten patients (mean age: 38.2 years) with severe acute ocular involvement but no long-term sequelae [48], all patients received systemic corticosteroid pulse therapy, followed by an average initial dosage of 1.5 mg/kg/day of prednisolone equivalent, which was tapered based on their clinical responses. Systemic corticosteroids were discontinued for an average of 26 days (range: 12–60 days) after pulse therapy.

Topical treatment included 0.1% betamethasone eye drops administered nine times daily and betamethasone eye ointment applied twice daily. Systemic corticosteroids were tapered starting from the second week; however, topical steroids were tapered from the third week. Elevated levels of inflammatory cytokines in tear fluid were detected even after systemic inflammation subsided, which was consistent with clinical observations. These findings support the need for the extended use of topical anti-inflammatory therapy.

11 | CQ11: What Other Organs Are Affected Besides the Skin and Mucous Membranes?

Recommendation Statement: Severe pneumonia, gastrointestinal symptoms, and renal impairment may occur.

Explanation

In SJS/TEN, organs other than the skin and mucous membranes that are reported to be affected include the lungs, digestive tract, liver, and kidneys. Respiratory disorders, including pneumonia and interstitial pneumonia, have been reported to occur in approximately 23% of cases [49]. In severe cases, patients who develop acute respiratory distress syndrome often require a ventilator [49]. In a previous study by Yamane et al. involving 52 SJS and 35 TEN cases in Japan [50], the prevalence rates of respiratory diseases, including laryngeal edema, were 3.8% and 8.6% in SJS and TEN cases, respectively. In a nationwide survey (2016–2018) conducted by the Severe Erythema Multiforme Study Group of the Ministry of Health, Labor, and Welfare, 49 (12.5%) of 392 cases analyzed developed respiratory diseases. Oxygen therapy was initiated in 48 cases, with 13 cases requiring a ventilator. Bronchiolitis obliterans, which is a rare complication of SJS/TEN, has been reported in some cases, with subacute respiratory failure occurring early in the disease and symptoms gradually worsening over several years [50]. In severe cases, lung transplantation may be indicated; thus, collaboration with a pulmonary specialist is important. For information on the diagnosis and treatment of bronchiolitis obliterans, please refer to the "Guidelines for the Treatment of Refractory Diffuse Lung Diseases" edited by the Japanese Respiratory Society [51].

Previously, renal and hepatic dysfunctions have each been associated with the onset of new respiratory diseases and exhibit poor prognoses [7]. Among the 12 patients in this study who underwent hemodialysis during the course of the disease, five survived and seven died [7]. In addition, one case of drug-induced vanishing bile duct syndrome was observed. Liver failure is

categorized into acute liver failure, characterized by rapid loss and necrosis of hepatocytes, and chronic liver failure, where cholangitis leads to the loss of bile ducts and results in cholestatic cirrhosis. Reports of drug-induced vanishing bile duct syndrome associated with SJS/TEN are rare. There have been only 15 such cases, with eight studies on pediatric cases. Among the 15 cases, nine underwent liver transplantation with a poor prognosis or died [52]. Among the 392 cases analyzed in the national survey of SJS/TEN [7], 135 (34.4%) had liver damage at the time of their final dermatology visit (median of 47 days after onset). One case required liver transplantation due to acute liver failure [53], and one case experienced drug-induced vanishing bile duct syndrome. Compared to cases with alanine aminotransferase (ALT) levels of > 100 IU/L at the peak of the disease, cases with total bilirubin (T-Bil) of ≥ 1.3 mg/dL had a poorer prognosis. Cases with ALT > 100 IU/L and T-Bil ≥ 1.3 mg/dL had a mortality rate of approximately 40% at 1 month post-onset, indicating an even poorer prognosis.

The kidneys are affected by pre-renal failure caused by a decrease in blood circulation due to epidermal cell necrosis. Additionally, drug-induced renal failure may be caused by toxicity, allergic or immunological reactions, urinary tract obstruction, and other mechanisms. The pathological conditions associated with renal failure include interstitial damage, tubular damage or obstruction, and glomerular damage. Risk factors for the onset of acute renal failure include infections, such as sepsis, medications (allopurinol, antibiotics, and NSAIDs), chronic kidney disease, and hypoalbuminemia. Acute kidney injury is observed in approximately 19% of cases, with 15% and 5% of the cases requiring dialysis initiation and long-term dialysis, respectively [54]. Additionally, the significant predictors of mortality include infections (sepsis, pneumonia, tuberculosis, etc.), aging, chronic diseases, hematologic malignancies, and (acute) renal failure [55].

12 | CQ12: Which Treatments are Effective for SJS/TEN?

Recommendation Statement: Early administration of high-dose systemic corticosteroids and steroid pulse therapy is effective.

Explanation

In the second survey study, the ratio of the mortality rate predicted by the Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN) to the actual mortality rate was calculated by each treatment method. The mortality rate was significantly reduced by high-dose steroid therapy (rate: 0.40; 95% confidence interval [CI], 0.17–0.86), followed by steroid pulse therapy (rate: 0.52; 95% CI, 0.31–0.85), demonstrating the efficacy of both treatments. No significant differences were observed between the mortality rate predicted by the SCORTEN score and the actual mortality rate obtained for the treatment methods [7]. International studies have also indicated that steroid monotherapy improves skin re-epithelialization compared to supportive care and reduces the actual mortality rate compared to the SCORTEN-predicted mortality rate [56]. Additionally, some reports have suggested that combination therapy comprising corticosteroids and intravenous immunoglobulin improves the prognosis of SJS/TEN patients [56–58], and the efficacy of combination therapy is gaining attention.

13 | CQ13: When Should Steroid Pulse Therapy Be Selected?

Recommendation Statement: In SJS/TEN cases where the disease progresses rapidly, steroid pulse therapy should be considered with the aim of halting disease progression.

Explanation

Steroid pulse therapy is used in various immune-mediated diseases; however, there is a general consensus supporting its use in critical conditions requiring prompt improvement, such as rapid renal dysfunction, respiratory failure, or status epilepticus. Systemic steroid administration for SJS/TEN is associated with an increased risk of infection; however, no study has reported a higher mortality rate in these cases compared to cases receiving supportive care alone [59]. Previous case series have reported that steroid pulse therapy is effective in suppressing ocular lesions in SJS [47, 60]. In SJS/TEN patients with acute ocular lesions, steroid pulse therapy within 4 days of onset may reduce the risk of severe ocular sequelae [61]. Furthermore, an epidemiological survey conducted in Japan from 2016 to 2018 demonstrated that high-dose steroid and steroid pulse therapies considerably reduce the mortality rates [7].

Regarding systemic steroid administration for TEN, reports have suggested that it increases the risk of infection and prolongs hospitalization [61], whereas others indicated that steroid pulse therapy did not prolong the healing time and was associated with reduced mortality [62]. Steroid pulse therapy should be considered for severe cases, rapidly progressing cases, or cases with mild rash but severe ocular symptoms. However, in cases where epidermal detachment has progressed to extensive erosion, caution is warranted as it may increase the risk of infection and inhibit epidermal regeneration.

The treatment algorithm for SJS/TEN is shown in Figure 2.

14 | CQ14: Is There an Overlap Between SJS/TEN and Drug-Induced Hypersensitivity Syndrome (DIHS)?

Recommendation Statement: When the skin symptoms fulfill the diagnostic criteria for SJS or TEN and also meet the diagnostic criteria for DIHS, it is referred to as an overlap between SJS/TEN and DIHS. Although rare, an overlap between the two diseases does occur.

Explanation

DIHS is a drug rash characterized by delayed onset and rapid progression. It is caused by a limited range of causative drugs. This condition is primarily diagnosed via clinical course and laboratory findings of a patient, such as late onset, prolonged disease course, high fever, multi-organ damage, and reactivation of human herpesvirus 6. Contrarily, SJS/TEN is diagnosed via skin

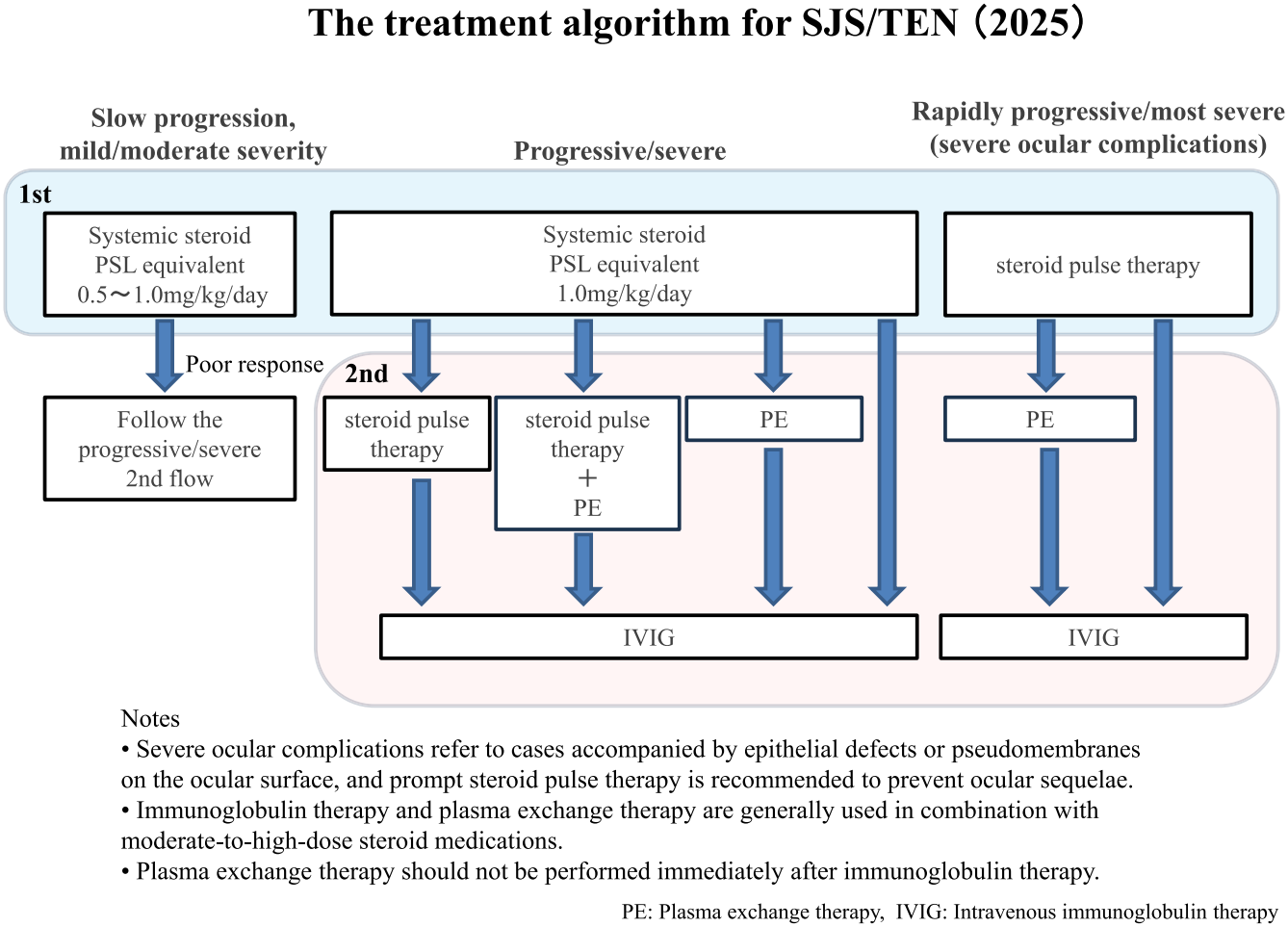

FIGURE 2 | The treatment algorithm for SJS/TEN (2025). This algorithm outlines a step-wise treatment approach for Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), based on the clinical severity and progression of the disease. Initial treatment is chosen according to the severity of the case. Moderate cases are treated with systemic corticosteroids at 0.5–1.0 mg per kg per day (prednisolone equivalent), whereas rapidly progressive or severe cases require prompt initiation of steroid pulse therapy. In cases with severe ocular involvement, such as corneal epithelial defects or formation of pseudomembranes, early administration of steroid pulse therapy is strongly recommended to reduce the risk of future complications. If the response to the initial treatment is insufficient or the disease continues to progress, second-step therapies, including steroid pulse therapy, plasma exchange (PE), and intravenous immunoglobulin (IVIG), should be commenced without delay. PE and IVIG should always be used in combination with systemic corticosteroids at moderate or high doses. PE should not be performed immediately after IVIG administration, as it may remove the infused immunoglobulin.

findings. Therefore, there are cases that meet the diagnostic criteria for DIHS while also fulfilling the criteria for SJS/TEN; such a scenario is referred to as an overlap [63]. In most cases with an overlap, DIHS precedes, and during the course of the disease, SJS/TEN-like symptoms, such as blisters and lip ulcers, may develop. Skin symptoms of SJS/TEN may appear early in the course of DIHS [63–66] or develop as skin symptoms during a relapse of DIHS [67–69]. The incidence of such overlap is rare; in a national epidemiological survey of DIHS conducted in 2021, ten (3.4%) out of 293 DIHS cases were found to overlap with SJS/TEN. The rash in DIHS typically presents as disseminated erythematous papules or polymorphic erythema and may progress to erythroderma. Histopathologically, DIHS is characterized by marked inflammatory cell infiltration in the dermis, with mild but variable interface dermatitis findings and, occasionally, severe epidermal damage leading to SJS/TEN. Additionally, while mucosal involvement might occur in DIHS, it is typically mild, manifesting as erythema and mild erosion of the oral mucosa and lips. However, in rare cases, extensive and severe erosive ulcers may form, and when they are accompanied by erosion of the genitalia and conjunctival hyperemia, the criteria for SJS are met. Ocular involvement is often limited to conjunctival injection, but some cases may leave sequelae, such as dry eye or scarring conjunctivitis [65, 70]. The mechanism underlying the overlap remains unclear; however, the recurrence of DIHS rash may progress to SJS/TEN, and NSAIDs administered during DIHS treatment or prophylactic medications given for opportunistic infections may potentially trigger the onset of SJS/TEN.

15 | CQ15: Is the New Prognostic Prediction Score, Clinical Risk Score for Toxic Epidermal Necrolysis (CRISTEN), effective for SJS/TEN?

Recommendation Statement: Cristen has been proposed as a prognostic factor for SJS/TEN and may be useful.

TABLE 2 | A new prognostic prediction score called CRISTEN.

	Parameter	Detailed definitions
1	Age, ≥ 65 years	
2	Epidermal detachment of > 10% of BSA	
3	Malignant neoplasm	Active phase
4	Diabetes mellitus	Under treatment with medication (not including those undergoing dietary counseling only)
5	Renal impairment	Chronic kidney disease
6	Bacterial infection	Pneumonia, sepsis, and urinary-tract infection (not including mild colds or upper respiratory tract inflammation)
7	Cardiac disease	Heart failure, valvular disease, arrhythmias, aortic aneurysms, angina, atrial and ventricular septal defects, and hypertension under treatment
8	Antibiotics in the culprit drugs	
9	Mucosal damage affecting all three of ocular, buccal, and genital mucosa	
10	Systemic corticosteroid therapy prior to the onset of SJS/TEN	Regardless of dose or duration of administration

Sum of score	Mortality rate (%)
10	
9	
8	100
7	66.7
6	61.1
5	50
4	20.8
3	13.2
2	3.4
1	1.2
0	0

Note: Description of each CRISTEN parameter and estimated mortality rate based on the total score. Parameters are based on clinical findings and medical history at the time of the initial presentation. Each parameter is assigned to 1 point, and the total score is used to estimate the mortality rate.

Explanation

The most well-known prognostic prediction score for SJS/TEN that has been widely used to date is SCORTEN (TEN-specific severity illness score) [71]. This scale was published in 2000 and includes several factors, including age, epidermal detachment area, concomitant malignant tumors, tachycardia, HCO_3^- levels, and blood levels of glucose and urea nitrogen. The estimated mortality rate can be predicted based on the total score. Although this scoring system is still widely used globally, it requires blood gas measurement and is composed of several parameters, including heart rate and blood glucose levels, which can fluctuate. A recent study suggested that SCORTEN may overestimate or underestimate the mortality rates [72]. Therefore, based on the data from 382 cases identified in the second national survey of SJS/TEN in Japan, a new prognostic prediction score called CRISTEN was proposed. This scoring system selects ten factors with high odds ratios for mortality and assigns one point to each [73]. The ten items in CRISTEN comprise clinical findings and medical history at the initial visit, including age, epidermal detachment area, concomitant malignant tumors, diabetes, renal dysfunction, bacterial infections, cardiovascular diseases, use of antibiotics as the causative drug, mucosal damage in all three areas (eyes, mouth, and genitalia), and history of systemic steroid therapy (Table 2). The predictive accuracy of CRISTEN in Japan is high, with an area under the curve (AUC) of 0.876. Furthermore, validation using 415 cases across seven countries also confirmed an AUC of 0.827, demonstrating that the efficacy of CRISTEN was comparable to that of existing prognostic prediction scores. CRISTEN is considered a simple and useful indicator as all of its components are based solely on the initial clinical findings and medical history. However, further accumulation of cases is necessary for its future use.

TABLE 3 | Diagnostic criteria for SJS/TEN 2025.

Diagnostic criteria for SJS (the Japanese SJS/TEN guideline criteria)	
Major criteria (Required)	
1	Extensive and severe mucosal lesions (e.g., erosions with bleeding or crusting) at the mucocutaneous junctions (eyes, oral cavity genitalia, etc.).
2	Presence of widespread erythema accompanied by erosions or blisters resulting from necrotic damage to the epidermis. After resolution, crusts or membranous desquamation are observed. The affected area covers less than 10% of the body surface area (BSA). However, areas where the epidermis is likely to detach easily under slight pressure are included in this measurement.
3	Presence of fever.
4	Histopathological examination reveals necrotic changes in the epidermis[†].
5	Exclusion of erythema multiforme major (EMM)[‡], and skin disorders caused by pharmacological effects of cytotoxic anticancer drugs, not delayed-type allergies.
Minor criteria	
1	Erythema is distributed systemically, predominantly on the face, neck, and trunk. The erythema is non-elevated, shows centrally dark-red flat atypical targets, and tends to coalesce.
2	Mucosal lesions at the mucocutaneous junctions are present. Ocular involvement includes bilateral acute conjunctivitis with pseudomembrane formation and/or epithelial defects on the ocular surface.
3	Systemic symptoms include observable severity and subjective fatigue. Due to oral and pharyngeal pain, varying degrees of feeding difficulties are present.
4	Exclusion of autoimmune blistering diseases.
Diagnosis	
A diagnosis of SJS is made when all five major criteria are met, considering the minor criteria as well. The evaluation should encompass the entire clinical course, not just the initial assessment.	
Notes:	
1	Differentiation from EMM should be based on a comprehensive assessment, including the major criteria (1)–(5), severity and fatigue, response to treatment, and histopathological findings of epidermal necrosis.
2	[†]In fully developed cases, histopathology shows full-thickness epidermal necrosis; it is desirable to confirm at least 10 necrotic keratinocytes per 200× magnification field.
3	[‡]EMM refers to erythema multiforme with relatively mild mucosal involvement. Lesions are primarily distributed on the extremities. While systemic symptoms like fever are common, they are less severe. EMM is a distinct condition from SJS.
4	Rarely, SJS may present solely with mucosal lesions.

(Continues)

TABLE 3 | (Continued)

Diagnostic criteria for TEN (the Japanese SJS/TEN guideline criteria) 2025	
Major criteria (Required)	
1	Extensive erythema accompanied by blisters and erosions affecting more than 10% of the body surface area (BSA). Areas where the epidermis is likely to detach easily under slight pressure are included in this measurement. According to international standards, epidermal detachment involving 10%–30% of the BSA may be diagnosed as SJS/TEN overlap.
2	Presence of fever.
3	Exclusion of acute generalized exanthematous pustulosis, autoimmune blistering diseases, staphylococcal scalded skin syndrome, toxic shock syndrome, and impetigo and skin disorders caused by pharmacological effects of cytotoxic anticancer drugs, not delayed-type allergies.
Minor criteria	
1	Initial lesions are widespread macular erythema, characterized by non-elevated, centrally dark-red flat atypical targets or diffuse erythema. The erythema predominantly affects the face, neck, and trunk.
2	Mucosal lesions at mucocutaneous junctions are present. Ocular involvement includes bilateral acute conjunctivitis with pseudomembrane formation and/or epithelial defects on the ocular surface.
3	Systemic symptoms include observable severity and subjective fatigue. Due to oral and pharyngeal pain, varying degrees of feeding difficulties are present.
4	Histopathological examination reveals necrotic changes in the epidermis. In fully developed cases, full-thickness epidermal necrosis is observed; even in mild lesions, it is desirable to confirm at least 10 necrotic keratinocytes per 200× magnification field.
Diagnosis	
A diagnosis of TEN is made when all three major criteria are met, considering the minor criteria as well. The evaluation should encompass the entire clinical course for a comprehensive assessment.	
Notes:	
1	Subtype classification: ・SJS progression type (TEN with spots, TEN with macules) Diffuse erythema progression type (TEN without spots, TEN on large erythema) ・Special type: Cases progressing from multiple fixed drug eruptions, etc.
2	In cases beginning with diffuse erythema, if the area of epidermal detachment does not reach 10% of the BSA due to treatment modifications, it is considered an incomplete type.

Note: SJS was diagnosed when all five major criteria were met. TEN was diagnosed based on three major criteria, including the extent of skin detachment and exclusion of other conditions. Minor criteria were considered supportive. Diagnosis was made based on the full clinical course. Notes provide additional details on differential diagnosis, histology, and subtype classification.

16 | CQ16: Are there any cases that differ from delayed-type hypersensitivity among the skin reactions reported as SJS/TEN following the introduction of newly developed drugs?

Recommendation Statement: There are cases that are not delayed-type hypersensitivity.

Explanation

Among the cases diagnosed as SJS/TEN based on epidermal detachment following anti-cancer drug administration, some cases of epidermal detachment are believed to emerge due to pharmacological effects rather than from a delayed-type hypersensitivity reaction. These cases should not be classified as true SJS/TEN. For example, enfortumab vedotin is a conjugate of an anti-Nectin-4 antibody and monomethyl auristatin E (MMAE). Given that nectin-4 is also expressed in epidermal keratinocytes, MMAE, a microtubule inhibitor, directly induces epidermal damage [74]. In severe cases, the clinical presentation might resemble SJS/TEN [74–76], but the underlying mechanisms differ from those of true SJS/TEN, and it is important to avoid diagnosing it as SJS/TEN solely based on epidermal detachment. Recently, the number of such case reports has been increasing, and the 2025 SJS/TEN diagnostic criteria have added "skin damage caused by the pharmacological effects of cytotoxic anticancer agents, not delayed-type hypersensitivity" as a condition to be excluded from the major findings (Table 3). In cases of skin damage caused by the pharmacological effects of cytotoxic anticancer agents, systemic administration of high-dose corticosteroids or immunosuppressants should not be easily performed; instead, supportive therapy (topical corticosteroids, oral antihistamines, and so on) should be considered.

17 | CQ17: Is Etanercept Effective?

Recommendation Statement: In patients with moderate to severe SJS/TEN or those with insufficient re-epithelialization following corticosteroid monotherapy, co-administration of etanercept with corticosteroids is recommended as it may lead to the acceleration of re-epithelialization, reduction of the total steroid dosage, and a decrease in mortality. Its use is weakly recommended (strength of recommendation: weakly recommended, evidence level: III).

Explanation

Based on the evidence that TNF-α is involved in the pathogenesis of epidermal cell (necrotic) death in SJS/TEN, treatment with the TNF-α inhibitor etanercept has been performed, and numerous reports have been published.

A single-center prospective randomized controlled trial (RCT) in Taiwan including 96 patients compared the etanercept group with the corticosteroid group. Compared to the corticosteroid monotherapy group, the etanercept group showed a shortened skin healing time of 19 days and 14 days in moderate and severe cases, respectively ($p = 0.010$). Although the reduction was not statistically significant, the predicted mortality rate decreased from 17.7% to 8.3% (56).

Furthermore, a multicenter observational study (242 cases) reported that the etanercept combination group showed statistically significant improvements in both mortality and time to skin healing compared with the corticosteroid monotherapy group [77].

A meta-analysis review also suggested that TNF-α inhibitors, including etanercept, may contribute to promote re-epithelialization and reduce mortality in SJS/TEN patients [78].

Moreover, a specific clinical trial (a category of regulated clinical research under Japan's Clinical Trials Act) conducted in Japan reported that for cases with poor response to corticosteroid therapy, the combination use of etanercept (50 mg/week, maximum 3 times) resulted in a shorter median time to re-epithelialization of 10 days (mean 12.8 days) compared to previous reports of corticosteroid monotherapy. Adverse events were only mild to moderate, with no fatalities [79].

Consistent with these and other reports, the shortening of skin re-epithelialization and the reduction of the total corticosteroid dosage are confirmed across multiple studies, supporting the effectiveness in moderate to severe cases. Furthermore, a tendency towards decreased predicted mortality was observed in many reports. Crucially, no increase in severe adverse effects was noted; rather, there was a tendency for them to decrease compared to the corticosteroid monotherapy group.

On the other hand, etanercept monotherapy is currently not the primary approach due to limited data comparing its efficacy with corticosteroid combination therapy; the latter remains the current standard. Patient selection primarily involves moderate to severe cases with a BSA of $\geq 10\%$, or cases that are corticosteroid-refractory or at high risk for corticosteroid side effects. Furthermore, large-scale RCTs have not yet been conducted, and the implementation of multicenter randomized trials is desired.

Note that etanercept is not approved for this indication in Japan (as of September 2025). Since it is also not covered by health insurance, full explanation and consent are required for its use.

This is the secondary publication of the paper that was published in Vol. 135, Iss. 4, pages 701–714, doi: 10.14924/dermatol.135.701 of the Japanese Journal of Dermatology. The authors have obtained permission for secondary publication from the Editor of the Japanese Journal of Dermatology. All co-authors have given their consent to the secondary publication of this work.

These guidelines are a consolidated version of the Japanese edition "Guidelines for the Management of Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis 2025 Supplement" and its addendum.

Funding

This study was supported by the Health and Labor Sciences Research Grants from the Ministry of Health, Labor, and Welfare of Japan (R5-nanchi[nan]-ippan-081) under grant number JPMH23FC1038 to R.A.

Conflicts of Interest

Riichiro Abe Is an Editorial Board Member of the Journal of Dermatology and a co-author of this article. To minimize bias, he was excluded from all editorial decision-making related to the acceptance of this article for publication. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. W. H. Chung, S. I. Hung, J. Y. Yang, et al., "Granulysin Is a Key Mediator for Disseminated Keratinocyte Death in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis," *Nature Medicine* 14, no. 12 (Level IVb) (2008): 1343–1350, https://doi.org/10.1038/nm.1884.

2. R. Abe, T. Shimizu, A. Shibaki, H. Nakamura, H. Watanabe, and H. Shimizu, "Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome Are Induced by Soluble Fas Ligand," *American Journal of Pathology* 162 (Level IVb) (2003): 1515–1520.

3. N. Saito, H. Qiao, T. Yanagi, et al., "An Annexin A1-FPR1 Interaction Contributes to Necroptosis of Keratinocytes in Severe Cutaneous Adverse Drug Reactions," *Science Translational Medicine* 6, no. 245 (Level IVb) (2014): 245ra95, https://doi.org/10.1126/scitranslmed.3008227.

4. M. Kinoshita, Y. Ogawa, N. Hama, et al., "Neutrophils Initiate and Exacerbate Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis," *Science Translational Medicine* 13, no. 600 (Level IVb) (2021): eaax2398, https://doi.org/10.1126/scitranslmed.aax2398.

5. I. Viard-Leveugle, O. Gaide, D. Jankovic, et al., "TNF-α and IFN-γ Are Potential Inducers of Fas-Mediated Keratinocyte Apoptosis Through Activation of Inducible Nitric Oxide Synthase in Toxic Epidermal Necrolysis," *Journal of Investigative Dermatology* 133, no. 2 (Level IVb) (2013): 489–498, https://doi.org/10.1038/jid.2012.330.

6. Y. Kida, K. Kuwano, Y. Zhang, and S. Arai, "*Acholeplasma Laidlawii* Up-Regulates Granulysin Gene Expression via Transcription Factor Activator Protein-1 in a Human Monocytic Cell Line, THP-1," *Immunology* 104, no. 3 (Level IVb) (2001): 324–332, https://doi.org/10.1046/j.1365-2567.2001.01310.x.

7. Y. Sunaga, M. Kurosawa, H. Ochiai, et al., "The Nationwide Epidemiological Survey of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Japan, 2016-2018," *Journal of Dermatological Science* 100, no. 3 (Level IVb) (2020): 175–182.

8. S. Kitami, H. Watanabe, H. Sueki, et al., "Nationwide Epidemiological Survey of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Research Project on Severe Erythema Multiforme Supported by the Ministry of Health, Labour and Welfare Research on Rare and Intractable Diseases, in 2008," *Japanese Journal of Dermatology* 121 (Japanese) (Lebel IVb) (2011): 2467–2482.

9. W. H. Chung, S. I. Hung, H. S. Hong, et al., "Medical Genetics: A Marker for Stevens-Johnson Syndrome," *Nature* 428, no. 6982 (Level IVb) (2004): 486.

10. C. B. Man, P. Kwan, L. Baum, et al., "Association Between HLA-B*1502 Allele and Antiepileptic Drug-Induced Cutaneous Reactions in Han Chinese," *Epilepsia* 48, no. 5 (Level IVb) (2007): 1015–1018.

11. C. Locharernkul, J. Loplumlert, C. Limotai, et al., "Carbamazepine and Phenytoin Induced Stevens-Johnson Syndrome Is Associated With HLA-B*1502 Allele in Thai Population," *Epilepsia* 49, no. 12 (Level IVb) (2008): 2087–2091.

12. C. C. Chang, C. L. Too, S. Murad, and S. H. Hussein, "Association of HLA-B*1502 Allele With Carbamazepine-Induced Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome in the Multi-Ethnic Malaysian Population," *International Journal of Dermatology* 50, no. 2 (Level IVb) (2011): 221–224.

13. N. Kaniwa, Y. Saito, M. Aihara, et al., "HLA-B*1511 Is a Risk Factor for Carbamazepine-Induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Japanese Patients," *Epilepsia* 51, no. 12 (Level IVb) (2010): 2461–2465.

14. K. Fukunaga, E. Tsukagoshi, M. Kurata, et al., "Differential Effects of HLA-B15:11 and HLA-A31:01 on Carbamazepine-Induced Cutaneous Adverse Reactions," *Journal of Investigative Dermatology* 144, no. 4 (Level IVb) (2024): 908–911.

15. S. I. Hung, W. H. Chung, L. B. Liou, et al., "HLA-B*5801 Allele as a Genetic Marker for Severe Cutaneous Adverse Reactions Caused by Allopurinol," *Proceedings of the National Academy of Sciences of the United States of America* 102, no. 11 (Level IVb) (2005): 4134–4139.

16. C. Lonjou, N. Borot, P. Sekula, et al., "A European Study of HLA-B in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Related to Five High-Risk Drugs," *Pharmacogenetics and Genomics* 18, no. 2 (Level IVb) (2008): 99–107.

17. M. Tohkin, N. Kaniwa, Y. Saito, et al., "A Whole-Genome Association Study of Major Determinants for Allopurinol Related Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Japanese Patients," *Pharmacogenomics Journal* 13, no. 1 (Level IVb) (2013): 60–69.

18. M. Ueta, K. Tokunaga, C. Sotozono, et al., "HLA-A*0206 With TLR3 Polymorphisms Exerts More Than Additive Effects in Stevens-Johnson Syndrome With Severe Ocular Surface Complications," *PLoS One* 7, no. 9 (Lebel IVb) (2012): e43650.

19. N. Kaniwa, E. Sugiyama, Y. Saito, et al., "Specific HLA Types Are Associated With Antiepileptic Drug-Induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Japanese Subjects," *Pharmacogenomics* 14, no. 14 (Level IVb) (2013): 1821–1831.

20. W. Manuyakorn, K. Siripool, W. Kamchaisatian, et al., "Phenobarbital-Induced Severe Cutaneous Adverse Drug Reactions Are Associated With CYP2C19*2 in Thai Children," *Pediatric Allergy and Immunology* 24, no. 3 (Level IVb) (2013): 299–303.

21. S. C. Su, C. G. Chen, W. C. Chang, et al., "HLA Alleles and CYP2C9*3 as Predictors of Phenytoin Hypersensitivity in East Asians," *Clinical Pharmacology and Therapeutics* 105, no. 2 (Level IVb) (2019): 476–485.

22. W. H. Chung, W. C. Chang, Y. S. Lee, et al., "Genetic Variants Associated With Phenytoin-Related Severe Cutaneous Adverse Reactions," *Jama* 312, no. 5 (Level IVb) (2014): 525–534.

23. Y. Deng, S. Li, L. Zhang, H. Jin, and X. Zou, "Association Between HLA Alleles and Lamotrigine-Induced Cutaneous Adverse Drug Reactions in Asian Populations: A Meta-Analysis," *Seizure* 60 (Level IVb) (2018): 163–171.

24. R. Nakamura, T. Ozeki, N. Hirayama, et al., "Association of HLA-A*11:01 With Sulfonamide-Related Severe Cutaneous Adverse Reactions in Japanese Patients," *Journal of Investigative Dermatology* 140, no. 8 (Level IVb) (2020): 1659–1662.

25. K. Fukunaga, E. Tsukagoshi, M. Kurata, et al., "Association of HLA-A11:01, HLA-B39:01 and HLA-B*56:03 With Salazosulfapyridine-Induced Cutaneous Adverse Drug Reactions," *Journal of Allergy and Clinical Immunology: In Practice* 12, no. 5 (Level IVb) (2024): 1355–1358.

26. Y. Sunaga, N. Hama, H. Ochiai, et al., "Risk Factors for Sepsis and Effects of Pretreatment With Systemic Steroid Therapy for Underlying Condition in SJS/TEN Patients: Results of a Nationwide Cross-Sectional Survey in 489 Japanese Patients," *Journal of Dermatological Science* 107, no. 2 (Level IVb) (2022): 75–81.

27. M. Ziemer, S. H. Kardaun, Y. Liss, and M. Mockenhaupt, "Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Patients With Lupus Erythematosus: A Descriptive Study of 17 Cases From a National

Registry and Review of the Literature," *British Journal of Dermatology* 166, no. 3 (Level IVb) (2012): 575–600.

28. N. Mittmann, S. R. Knowles, M. Koo, N. H. Shear, A. Rachlis, and S. B. Rourke, "Incidence of Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome in an HIV Cohort: An Observational, Retrospective Case Series Study," *American Journal of Clinical Dermatology* 13, no. 1 (Level IVb) (2012): 49–54.

29. C. Weinand, W. Xu, W. Perbix, et al., "27 Years of a Single Burn Centre Experience With Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Analysis of Mortality Risk for Causative Agents," *Burns* 39, no. 8 (Level IVb) (2013): 1449–1455.

30. Y. Yamane, S. Matsukura, Y. Watanabe, et al., "Retrospective Analysis of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in 87 Japanese Patients—Treatment and Outcome," *Allergology International* 65, no. 1 (Level IVb) (2016): 74–81.

31. M. Ueta, C. Sotozono, M. Nakano, et al., "Association Between Prostaglandin E Receptor 3 Polymorphisms and Stevens-Johnson Syndrome Identified by Means of a Genome-Wide Association Study," *Journal of Allergy and Clinical Immunology* 126, no. 6 (Level IVb) (2010): 1218–1225.

32. C. Sotozono, M. Ueta, E. Nakatani, et al., "Predictive Factors Associated With Acute Ocular Involvement in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis," *American Journal of Ophthalmology* 160, no. 2 (Level V) (2015): 228–237.

33. M. Ueta, C. Inoue, M. Nakata, et al., "Severe Ocular Complications of SJS/TEN and Associations Among Pre-Onset, Acute, and Chronic Factors: A Report From the International Ophthalmology Collaborative Group," *Frontiers in Medicine* 10 (Level IVb) (2023): 1189140.

34. M. Ueta, T. Matsuoka, S. Narumiya, and S. Kinoshita, "Prostaglandin E Receptor Subtype EP3 in Conjunctival Epithelium Regulates Late-Phase Reaction of Experimental Allergic Conjunctivitis," *Journal of Allergy and Clinical Immunology* 123, no. 2 (Level V) (2009): 466–471.

35. T. Honda, T. Matsuoka, M. Ueta, K. Kabashima, Y. Miyachi, and S. Narumiya, "Prostaglandin E(2)–EP(3) Signaling Suppresses Skin Inflammation in Murine Contact Hypersensitivity," *Journal of Allergy and Clinical Immunology* 124, no. 4 (Level V) (2009): 809–818.

36. M. Ueta, C. Sotozono, N. Yokoi, T. Inatomi, and S. Kinoshita, "Prostaglandin E Receptor Subtype EP3 Expression in Human Conjunctival Epithelium and Its Changes in Various Ocular Surface Disorders," *PLoS One* 6, no. 10 (Level IVb) (2011): e25209.

37. M. Ueta, H. Nishigaki, S. Komai, et al., "Positive Regulation of Innate Immune Response by miRNA-Let-7a-5p," *Frontiers in Genetics* 13 (Level IVb) (2023): 1025539.

38. M. Ueta, H. Nishigaki, K. Mizushima, Y. Naito, C. Sotozono, and S. Kinoshita, "Regulation of Innate Immune Response by miR-628-3p Upregulated in the Plasma of Stevens-Johnson Syndrome Patients," *Ocular Surface* 21 (Level IVb) (2021): 174–177.

39. M. Ueta and S. Kinoshita, "Ocular Surface Inflammation Is Regulated by Innate Immunity," *Progress in Retinal and Eye Research* 31, no. 6 (Level IVb) (2012): 551–575.

40. C. Sotozono, N. Yamauchi, S. Maeda, and S. Kinoshita, "Tear Exchangeable Limbal Rigid Contact Lens for Ocular Sequelae due to Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis," *American Journal of Ophthalmology* 158, no. 6 (Level IVb) (2014): 983–993.

41. M. Itoi, M. Ueta, K. Ogino, et al., "Clinical Trial to Evaluate the Therapeutic Benefits of Limbal-Supported Contact Lens Wear for Ocular Sequelae due to Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis," *Contact Lens & Anterior Eye* 43, no. 5 (Level IVb) (2020): 535–542.

42. Y. Yoshikawa, M. Ueta, S. Kinoshita, T. Kida, and C. Sotozono, "Long-Term Benefits of Tear Exchangeable Limbal-Rigid Contact Lens Wear Therapy in Stevens-Johnson Syndrome Cases," *Eye & Contact Lens* 49, no. 4 (Level IVb) (2023): 247–253.

43. C. Sotozono, T. Inatomi, T. Nakamura, et al., "Visual Improvement After Cultivated Oral Mucosal Epithelial Transplantation," *Ophthalmology* 120, no. 1 (Level IVb) (2013): 193–200.

44. Y. Aziza, M. Itoi, M. Ueta, T. Inatomi, S. Kinoshita, and C. Sotozono, "Limbal-Rigid Contact Lens Wear for the Treatment of Ocular Surface Disorders: A Review," *Eye & Contact Lens* 48 (Level IVb), no. 5 (2022): 313–317.

45. Y. Aziza, K. Imai, M. Itoi, et al., "Strategic Combination of Cultivated Oral Mucosal Epithelial Transplantation and Postoperative Limbal-Rigid Contact Lens-Wear for End Stage Ocular Surface Disease: A Retrospective Cohort Study," *British Journal of Ophthalmology* 108, no. 9 (Level IVb) (2024): 1177–1183.

46. F. Kinoshita, I. Yokota, H. Mieno, et al., "Multi-State Model for Predicting Ocular Progression in Acute Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis," *PLoS One* 16, no. 12 (Level IVb) (2022): e0260730.

47. Y. Araki, C. Sotozono, T. Inatomi, et al., "Successful Treatment of Stevens-Johnson Syndrome With Steroid Pulse Therapy at Disease Onset," *American Journal of Ophthalmology* 147, no. 6 (Level IVb) (2009): 1004–1011.

48. K. Matsumoto, M. Ueta, T. Inatomi, et al., "Topical Betamethasone Treatment of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis With Ocular Involvement in the Acute Phase," *American Journal of Ophthalmology* 253 (Level V) (2023): 142–151.

49. N. de Prost, A. Mekontso-Dessap, L. Valeyrie-Allanore, et al., "Acute Respiratory Failure in Patients With Toxic Epidermal Necrolysis: Clinical Features and Factors Associated With Mechanical Ventilation," *Critical Care Medicine* 42, no. 1 (Level V) (2014): 118–128.

50. Y. Kaneko, Y. Seko, C. Sotozono, et al., "Respiratory Complications of Stevens-Johnson Syndrome (SJS): Three Cases of SJS-Induced Obstructive Bronchiolitis," *Allergology International* 69, no. 3 (Level V) (2020): 465–467.

51. Committee for the Preparation of the Clinical Practice Guideline for Intractable Diffuse Lung Diseases, Study Group on Diffuse Lung Diseases, Research Project on Intractable Diseases, supported by the Ministry of Health, Labour and Welfare research on rare and intractable diseases, under the supervision of the Japanese Respiratory Society, "Clinical Practice Guideline for Intractable Diffuse Lung Diseases," 2017, Level I.

52. W. C. Lin, T. S. Hsieh, and C. Y. Chu, "Development of Vanishing Bile Duct Syndrome in Stevens-Johnson Syndrome Complicated by Hemophagocytic Lymphohistiocytosis," *Frontiers in Medicine* 9 (2022): 975754 (Level V).

53. M. Totsuka, T. Watanabe, N. Takamura, et al., "A Pediatric Case of Stevens-Johnson Syndrome With Acute Liver Failure, Resulting in Liver Transplantation," *Journal of Dermatology* 48, no. 10 (Level V) (2021): 1423–1427.

54. C. C. Hung, W. C. Liu, M. C. Kuo, C. H. Lee, S. J. Hwang, and H. C. Chen, "Acute Renal Failure and Its Risk Factors in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis," *American Journal of Nephrology* 29, no. 6 (Level IVb) (2009): 633–638.

55. D. Y. Hsu, J. Brieva, N. B. Silverberg, and J. I. Silverberg, "Morbidity and Mortality of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in United States Adults," *Journal of Investigative Dermatology* 136, no. 7 (2016 (Level IVb)): 1387–1397.

56. C. W. Wang, L. Y. Yang, C. B. Chen, et al., "Intravenous Immunoglobulin Combined With Corticosteroids for the Treatment of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis: A Propensity-Matched Retrospective Study in China," *Frontiers in Pharmacology* 12 (Level II) (2022): 750173.

57. R. G. Micheletti, Z. Chiesa-Fuxench, M. H. Noe, et al., "Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis: A Multicenter Retrospective Study of 377 Adult Patients From the United States," *Journal of Investigative Dermatology* 138, no. 11 (Level IVb) (2018): 2315–2321.

58. T. Y. Tsai, I. H. Huang, Y. C. Chao, et al., "Treating Toxic Epidermal Necrolysis With Systemic Immunomodulating Therapies: A Systematic Review and Network Meta-Analysis," *Journal of the American Academy of Dermatology* 84, no. 2 (Level I) (2021): 390–397.

59. S. Workswick and J. Cotliar, "Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Review of Treatment Options," *Dermatologic Therapy* 24, no. 3 (Level I) (2011): 207–218.

60. Y. Yamane, M. Aihara, S. Tatewaki, et al., "Analysis of Treatments and Deceased Cases of Severe Adverse Drug Reactions—Analysis of 46 Cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis," *Japanese Journal of Allergology* 58, no. 4 (Level IVb) (2009): 537–547.

61. P. H. Halebian, V. J. Corder, M. R. Madden, J. L. Finklestein, and G. T. Shires, "Improved Burn Center Survival of Patients With Toxic Epidermal Necrolysis Managed Without Corticosteroids," *Annals of Surgery* 204, no. 5 (Level IVb) (1986): 503–512.

62. S. H. Kardaun and M. F. Jonkman, "Dexamethasone Pulse Therapy for Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis," *Acta Dermato-Venereologica* 87, no. 2 (Level IVb) (2007): 144–148.

63. A. Casagranda, M. Suppa, F. Dehavay, and V. Del Marmol, "Overlapping DRESS and Stevens-Johnson Syndrome: Case Report and Review of the Literature," *Case Reports in Dermatology* 9, no. 1 (Level V) (2017): 1–7.

64. M. Tohyama and K. Hashimoto, "New Aspects of Drug-Induced Hypersensitivity Syndrome," *Journal of Dermatology* 38, no. 3 (Level IV) (2011): 222–228.

65. K. Hirose, Y. Matsudate, S. Tobita, et al., "A Case of Drug-Induced Hypersensitivity Syndrome With the Features of Toxic Epidermal Necrolysis," *Nishinihon Journal of Dermatology* 71, no. 6 (Japanese) (Level V) (2009): 584–588.

66. F. Oda, M. Fujiyama, A. Tokumaru, S. Murakami, and K. Hashimoto, "A Case of Overlapping Stevens-Johnson Syndrome and Drug-Induced Hypersensitivity Syndrome," *Practical Dermatology* 32, no. 7 (Japanese) (Level V) (2010): 895–898.

67. S. Kaneko, E. Morita, and Y. Tsugane, "Progression From Carbamazepine-Induced Drug-Induced Hypersensitivity Syndrome (DIHS) to Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) With Reactivation of HHV-6," *Visual Dermatology* 4, no. 10 (Japanese) (Level V) (2005): 1024–1025.

68. E. Mabuchi, M. Tsuji, Y. Ogido, and C. Uekami, "Drug-Induced Hypersensitivity Syndrome (DIHS) Showing Histological Features of Toxic Epidermal Necrolysis (TEN) During the Clinical Course," *Rinsho Derma* 51, no. 1 (Japanese) (Level V) (2009): 29–33.

69. H. Watanabe, R. Koide, and M. Iijima, "Toxic Epidermal Necrolysis Arising as a Sequela of Drug-Induced Hypersensitivity Syndrome," *Acta Dermato-Venereologica* 92, no. 2 (Level V) (2012): 214–215.

70. K. J. Bohm, J. B. Ciralsky, J. L. Harp, S. Bajaj, and K. C. Sippel, "Cicatrizing Conjunctivitis in a Patient Diagnosed With Drug Reaction With Eosinophilia and Systemic Symptoms/Drug-Induced Hypersensitivity Syndrome but With Features of Stevens-Johnson Syndrome," *Cornea* 35, no. 6 (Level V) (2016): 888–891.

71. S. Bastuji-Garin, N. Fouchard, M. Bertocchi, J. C. Roujeau, J. Revuvuz, and P. Wolkenstein, "SCORTEN: A Severity-of-Illness Score for Toxic Epidermal Necrolysis," *Journal of Investigative Dermatology* 115, no. 2 (Level IVb) (2000): 149–153.

72. I. Torres-Navarro, Á. Briz-Redón, and R. Botella-Estrada, "Accuracy of SCORTEN to Predict the Prognosis of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis: A Systematic Review and Meta-Analysis," *Journal of the European Academy of Dermatology and Venereology* 34, no. 10 (Level I) (2020): 2066–2077.

73. N. Hama, Y. Sunaga, H. Ochiai, et al., "Development and Validation of a Novel Score to Predict Mortality in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: CRISTEN," *Journal of Allergy and Clinical Immunology. Practice* 11, no. 10 (Level IVb) (2023): 3161–3168.

74. M. E. Lacouture, A. B. Patel, J. E. Rosenberg, and P. H. O'Donnell, "Management of Dermatologic Events Associated With the Nectin-4-Directed Antibody-Drug Conjugate Enfortumab Vedotin," *Oncologist* 27, no. 3 (Level V) (2022): e223–e232.

75. K. E. Hirotsu, J. Rana, J. Y. Wang, et al., "Clinicopathologic Characterization of Enfortumab Vedotin-Associated Cutaneous Toxicity in Patients With Urothelial Carcinoma," *Journal of the American Academy of Dermatology* 85, no. 6 (Level V) (2021): 1610–1611.

76. R. Sasaki, T. Fujimura, C. Lyu, and S. Aiba, "Severe Eczematoid and Lichenoid Eruption With Full-Thickness Epidermal Necrosis Developing From Metastatic Urothelial Cancer Treated With Enfortumab Vedotin," *Journal of Dermatology* 47, no. 12 (Level V) (2020): 1436–1438.

77. J. Zhang, C. W. Lu, C. B. Chen, et al., "Evaluation of Combination Therapy With Etanercept and Systemic Corticosteroids for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Multicenter Observational Study," *Journal of Allergy and Clinical Immunology. In Practice* 10, no. 5 (2022): 1295–1304.

78. J. Cao, X. Zhang, X. Xing, and J. Fan, "Biologic TNF-α Inhibitors for Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, and TEN-SJS Overlap: A Study-Level and Patient-Level Meta-Analysis," *Dermatology Ther. (Heidelb.)* 13, no. 6 (2023): 1305–1327.

79. H. Kimura, M. Oginezawa, N. Hama, et al., "Efficacy and Safety of Etanercept in Japanese Patients With Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Unresponsive to Systemic Steroid Therapy: A Multicenter, Open-Label, Single-Arm Study," *Journal of Dermatology* 52, no. 10 (2025): 1536–1544.