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Review Article

Liver Injury in Immune Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Five New Classification Types

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Abstract

Liver injury in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) is a multifaceted disorder, lacking cohort homogeneity due to a variety of potential causes, including drugs, arsenic and other heavy metals, glyphosate, infections, and ultraviolet radiation. The goals of this review were (1) to analyze the role of diagnostic algorithms in assessing causality for potential culprits involved in the development of liver injury associated with immune-mediated SJS and TEN, which represent immune-based variant disorders within a continuous spectrum. Milder forms are classified as SJS or SJS/TEN overlap, while TEN is known as the most serious form; and (2) to interpret the findings that allow for the characterization of the different types of these disorders. The manuscript is based on an extensive literature search for single case reports, case cohorts, and review articles. Search terms included: Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, and specific diagnostic algorithms such as the Roussel Uclaf Causality Assessment Method (RUCAM) and the Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN). For the purpose of basic feature description, the uniform term SJS/TEN is used in the current analysis. SJS/TEN presents with five different cohort types: SJS/TEN type (1), which refers to a cohort of SJS/TEN caused by drugs, as assessed by both ALDEN and RUCAM; type (2), representing SJS/TEN due to drugs and assessed by ALDEN only, but not by RUCAM; type (3), which includes a cohort of SJS/TEN caused by drugs, assessed by non-ALDEN and non-RUCAM tools; type (4), which focuses on a cohort of SJS/TEN caused by non-drug culprits, assessed by various tools; and type (5), which considers a cohort of SJS/TEN caused by unknown culprits. Using this new SJS/TEN typology will help better characterize individual features, personalize treatment, and clarify pathogenetic specifics for each of the five disease types. This new SJS/TEN typology provides clarity by replacing issues of inhomogeneity with cohort homogeneity.

Keywords: Stevens-Johnson syndrome; Toxic epidermal necrolysis; Stevens-Johnson syndrome/toxic epidermal necrolysis typology; Lyell syndrome; Orphan disease; the Algorithm of Drug Causality for Epidermal Necrolysis; ALDEN; the Roussel Uclaf Causality Assessment Method; RUCAM.

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Introduction

Historically, the surgeon Albert M. Stevens and the pediatrician Frank C. Johnson, both members of the staff at Bellevue Hospital in New York City, published a report entitled "A new eruptive fever associated with stomatitis and ophthalmia: Report of two cases in children" in the American Journal of Diseases of Children in December 1922.[1] More detailed summaries were later provided by the ophthalmologist Georg M. Bohigian, who focused on fever, conjunctivitis, inflamed mucous membranes, and total loss of vision affecting one boy.[2] In the original report, high and continuous fever was present in both patients. Sepsis with generalized eruptions was considered a possibility because, in the first boy, Staphylococcus aureus was detected in the necrotic center of one papule, although the blood culture was sterile, and in the second boy, the fever was attributed to pneumonia.[1] Finally, a skin eruption from drug ingestion was ruled out by careful inquiry, which showed that no drugs had been administered in either case.[1] The exact origin of the term "Stevens-Johnson syndrome" (SJS) and its acronym remains unclear.[2] In 1956, a condition known as toxic epidermal necrolysis (TEN) was identified in four patients by Alan Lyell,[3] later occasionally referred to as Lyell syndrome.[4] Diagnostic and management refinements were achieved by recognizing that SJS and TEN are primarily dermatologic disorders, now collectively termed SJS/TEN by convention.[5–7] SJS/TEN can easily be misdiagnosed as other dermatologic disorders with similar appearances that overlap in their diagnosis.[8–10]

In the following years, many efforts have been made to better understand specific issues related to SJS/TEN, which is now recognized as a multifaceted and complex disorder, as summarized in publications from 2023.[11–14] Topics of interest have included epidemiology, clinical features (including causative factors), differential diagnoses, symptoms, laboratory data, therapy options, prognosis, and the mechanistic steps leading to the disorder. However, an analysis of current data reveals that only parts of these findings are based on evidence from diagnostic algorithms. This shortcoming limits efforts to establish robust data on SJS/TEN and may make it difficult to compare results across various studies.

This article provides an overview of current developments in SJS/TEN, focusing on diagnostic algorithms applicable to SJS/TEN itself and the concomitant role of drugs as causative factors in drug-induced liver injury (DILI). The ultimate aim of the analysis was to provide a framework for SJS/TEN and associated DILI diagnoses that may help better characterize clinical features based on evidence.

Literature search

The literature search strategy included the PubMed database and Google Scholar, using the following terms: Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, the Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN), the Roussel Uclaf Causality Assessment Method (RUCAM), causality assessment, drugs, drug-induced liver injury, immunology, human leukocyte antigens (HLA), and combinations thereof. The obtained publications were checked for their suitability for inclusion in this review article and provided the primary basis for further analysis. The search was expanded to include reports referenced in the primary search and finalized on 25 June 2024. Publications were limited to those in the English language, with no other restrictions regarding the year of publication or study design.

Definitions

SJS and TEN

SJS is diagnosed when the skin reaction involves less than 10% of the body surface area (BSA), whereas TEN is characterized by skin reactions affecting more than 30% of the BSA. The intermediate form is classified when skin involvement is between 10–30%.[5,8,9,15] With the exception of BSA extension and severity grade, many features are similar among SJS, intermediate SJS/TEN, and TEN, which is why the three entities are collectively referred to as SJS/TEN,[5–7] Mainstream opinion also suggests that the intermediate form should be called SJS/TEN overlap.[8,16–18] In the past, the intermediate form was referred to as SJS/TEN,[19] but this term now conflicts with the identical expression used for another global condition, and should no longer be used for the sake of clarity. Features of SJS/TEN can be clearly described by considering data from cases with diagnoses verified through the use of the respective diagnostic algorithm.[20] To assess concomitant DILI, a different causality assessment method should be applied as a diagnostic algorithm.[21–23]

DILI

Increased liver tests (LTs) are commonly observed in patients with SJS/TEN and DILI. However, for these tests to qualify as indicators of DILI, certain thresholds must be met for serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP): more specifically, equal or greater than five times the upper limit of normal (ULN) for ALT or AST, and/or equal or greater than two times ULN for ALP.[22] Patients with LTs below the ULN threshold values do not have liver injury, but their values reflect liver adaptation or tolerance and could alternatively be considered as bystanders of liver disorders without clinical significance.[24,25]

Algorithms for causality assessment

Using validated causality assessment methods as diagnostic algorithms to confirm the diagnosis is essential for any disease. This approach is crucial for both SJS/TEN and associated DILI, as various conventional medications are suspected as causative drugs. These conditions provoke many differential diagnoses, making it initially difficult to find the correct diagnosis. To overcome these challenges, a diagnostic ALDEN was developed by an international group of experts led by Sassolas and colleagues from the Department of Dermatology, Centre Hospitalier Universitaire de Brest (France) in 2020.[20] Additionally, causality assessment for DILI in the implicated drug can be achieved using the RUCAM.[21–25] RUCAM was originally introduced in 1993 by Danan and Bénichou, based on results from international consensus meetings with participation from DILI experts worldwide.[21] The updated RUCAM version from 2016 is now the preferred too[22] and can help definitively identify a suspected drug as the cause in DILI and SJS/TEN.

The analysis of published reports on this subject revealed that diagnostic algorithms like ALDEN and RUCAM were applied in only a minority of cases, which limits the quality of published results regarding clinical features, causes, and pathophysiological aspects in this multifaceted disease complex. Despite these shortcomings, based on cases with appropriate causality assessments, various typical features have emerged as characteristics of this complex systemic orphan immune disorder spectrum. In future cases of suspected SJS/TEN, prospective causality assessment methods such as ALDEN and RUCAM should be applied early in the clinical management phase, as retrospective study designs often lead to incomplete case data, resulting in low causality grades due to missing essential diagnostic parameters.

ALDEN

ALDEN was conceptualized as a diagnostic algorithm for SJS/TEN, with a specific focus on medications as suspected culprit drugs.[20] It represents a validated, specific, reproducible, structured, and quantitative method using key items as individually scored elements. The sum of these scores ranges from −12 to 10, providing a final causality grading of very unlikely, unlikely, possible, probable, and very probable.[20] The six elements specifically include: (1) delay from initial drug intake to onset of reaction (index day); (2) drug present in the body on index day; (3) prechallenge/rechallenge; (4) dechallenge; (5) type of drug (notoriety); and (6) other cause.[20]

RUCAM

RUCAM has a long tradition as a diagnostic algorithm for assessing causality in cases of DILI and herb-induced liver injury (HILI).[21–25] This is evidenced by its application in 81,856 DILI cases and 14,029 HILI cases published worldwide by mid-2022, surpassing any other DILI algorithms in terms of case numbers.[26] Worldwide users appreciate the validated, specific, reproducible, structured, and quantitative diagnostic algorithm, which uses key elements that are individually scored.[22] Summing up the individual scores gives a final score for causality grading of excluded, unlikely, possible, probable, and highly probable for the suspected drug.[22] For hepatocellular liver injury, seven key elements are considered: (1) time to onset from the beginning of drug use; (2) course of ALT after cessation of the drug; (3) risk factors; (4) concomitant drug(s); (5) search for alternative causes; (6) previous hepatotoxicity; and (7) response to unintentional reexposure.[22] Of note, there are two types of the updated RUCAM: one for hepatocellular injury and another for cholestatic or mixed injury.[22]

The severity-of-illness score for toxic epidermal necrolysis (SCORTEN) for severity grading

Validated methods to quantify severity grades are available,

such as the SCORTEN, but this is only applicable for TEN. There have been attempts to establish prognostic scores to predict mortality in SJS/TEN,[27] but SCORTEN, the most renowned of such scores, was introduced by Bastuji-Garin et al. in 2000.[16] SCORTEN focuses on TEN and is a model consisting of seven individual risk factors for death.[16,27] These include patient age over 40, malignancies, tachycardia, initial extent of skin lesions, serum urea, as well as serum glucose and bicarbonate levels.[16] Cutoff points were proposed for each individual mortality risk factor, with deviations from the baseline adding one point to the score. A score of 1 point corresponds to a 3% mortality risk, while 5 points correspond to 85%, and more than 6 points correspond to 95%.[16,27] Some authors use SCORTEN not only to predict mortality but also to evaluate the efficacy of immunomodulatory treatments or supportive therapy.[27] However, there is evidence suggesting that SCORTEN tends to overestimate mortality risk in certain populations.

Epidemiology

In epidemiology, incidence reflects the number of new cases of a given medical condition in a population within a specified period of time, while *prevalence* refers to the proportion of a particular population affected by a medical condition at a specific time. The use of these criteria is essential in any epidemiological analysis, including those related to SJS/TEN, to ascertain the homogeneity of study cohorts and ensure comparative evaluations. Published epidemiological data on SJS/TEN vary among countries and regions, as summarized in 2024. It is also noted that the epidemiology of SJS/TEN in Asia is not well-documented, unlike in Europe and the United States of America(USA).[28] There is also variability in quality, as not a single study included cases assessed for causality using the diagnostic algorithm of ALDEN,[28–45] which was published only in 2010[20] and thus unavailable for reports that collected case data before that time. Additionally, the best results were obtained with SJS/TEN cases retrieved from a single dermatology center, rather than those collected retrospectively from national databases with inclusion criteria specific to SJS/TEN features. Major study limitations include the lack of standardization for diagnostic criteria, such as ALDEN. Epidemiological data lacking evaluation by ALDEN remain problematic. A critical overview of epidemiological details of SJS/TEN cases is presented for selected countries in alphabetical order.

Canada

In an observational, retrospective case series study in Canada, the focus was on epidemiological data related to SJS/TEN.[28] The study cohort included patients with human immunodeficiency virus (HIV), who were receiving HIV and HIV-related medications. Patients were retrieved from the database of the Ontario HIV Treatment Network, where diagnostic criteria for SJS and TEN were newly established. Two reviewers examined the medical records to confirm the diagnosis of SJS or TEN. Notably, the Canadian report used its own diagnostic criteria, which were published in 2012,[29] shortly after the ALDEN criteria became available in 2010.[20] The study found an incidence of SJS and/or TEN of five to seven per 3,710 or one to two per 1,000 individuals in the HIV cohort, which is consistent with previous results that reported incidences between 0.95 and one per 1,000 individuals with acquired immune deficiency syndrome.[28] Although the Canadian report provided some insight into the incidence range, the diagnostic approach was not ideal because a retrospective study design was used, and cases were retrieved from a database focusing on HIV but not necessarily on SJS/TEN.

China

A retrospective study in Hong Kong analyzed 125 cases of SJS/TEN during a 17-year study period, estimating an annual incidence of TEN alone at 1.36 cases per million, and a combined incidence of SJS, SJS/TEN overlap, and TEN at 5.07 cases per million.[29] These incidences were considered comparable to findings from studies in other countries. For the Hong Kong study, patients with clinical and histological diagnoses of SJS/TEN were analyzed. These patients had been treated at the Prince of Wales Hospital, a major regional hospital.[29] Patients were identified from the hospital database using the International Classification of Diseases codes and from the database of the Department of Anatomical and Cellular Pathology at the Prince of Wales Hospital. There was no explicit mention of using the ALDEN diagnostic algorithm.

Another publication from China titled "The Epidemiology of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in China",[30] presented a report with learning potential. According to this report, the incidence of SJS/TEN was analyzed in the admission database of the First Affiliated Hospital of Fujian Medical University, where 4,006 dermatology inpatients were treated during the study period from 2006 to 2016.[30] Drug causality was assessed using the ALDEN algorithm, and only cases with probable or definite scores were included in the analysis. To further analyze clinical characteristics, causality, and treatment outcomes for SJS/TEN in China, case reports from the China National Knowledge Infrastructure and Wanfang database from 2006 to 2016 were reviewed, as well as cases of patients with SJS/TEN admitted during the same period. The study enrolled 166 patients, including 70 with SJS, two with SJS/TEN overlap, and 94 with TEN. Details on various parameters, including mortality and the most common offending drugs, were provided—interesting data indeed. However, to the authors' surprise, the promised epidemiological data were not published, an omission not recognized by the authors, reviewers, or editor, and it was not corrected in the Erratum,[30] This lack of epidemiological data is why this report[30] was not discussed or quoted in the recent Hong Kong publication.[29]

France

In France, the nationwide annual incidence of TEN was retrospectively established over a five-year period at 1.2 cases per million.[28,31] Patient responses to TEN were analyzed, and validated cases were included in a study published in 1990,[31] which was 20 years prior to the publication of the ALDEN diagnostic algorithm.[20] An independent estimation derived from death certificates provided a figure of 1.3 cases per million per year.[31]

Another observational, non-interventional study in France retrospectively explored the epidemiology of SJS/TEN patients with bloodstream infections (BSI).[32] The rationale for this analysis was the observation that a special cohort of patients with TEN was described as a rare drug-related, life-threatening acute condition, with sepsis as the main cause of mortality due to skin colonization, which, on top of impaired barrier function, promotes BSI. The study included 179 patients, classified as having SJS (n = 54; 30.2%), SJS/TEN overlap (n = 59; 33.0%), and TEN (n = 66; 36.9%), with an in-hospital mortality of 13.4% (24/179). Forty-eight episodes of BSI occurred over an 11-year period, yielding a rate of 15.5/1,000 patient days.[32] The severity of SJS/TEN, but not its causality, was assessed using SCORTEN[16] as well as generic scores of organ dysfunction, including the Logistic Organ Dysfunction score[33] and the Simplified Acute Physiology Score II.[34] Surprisingly, the worldwide ALDEN

score, published in 2010,[20] was not applied, even though the study was performed at the national referral center for TEN, which is associated with dermatological and medical intensive care units at the 800-bed tertiary hospital in France, Hôpital Henri Mondor, Assistance Publique-Hôpitaux de Paris, Université Paris XII, Créteil. Case data were likely collected until 2010 when the report was finally published.[32]

Germany

In Germany, specifically in West Germany and West Berlin before reunification, the estimated overall annual incidence of SJS/TEN was 1.89 cases per one million inhabitants per year, assuming an average population of 64.5 million. Severe skin reactions were difficult to study due to the rarity of these diseases, with an incidence of about two cases per one million inhabitants per year.[33] Case data were retrieved from a registry structured as an intensive reporting system, regularly contacting more than 1,500 departments in hospitals with intensive care facilities or with more than 200 beds (n = 1,161). With a coverage rate of up to 95%, based on the number of responding departments between April 1, 1990, and December 31, 1992, a total of 767 cases were reported, and 353 patients were finally included in the registry.[35] The ALDEN diagnostic scoring method, published only in 2020,[20] was not applied in the German report, which was published in 1996.[33]

Another study from Germany on the epidemiology of SJS/TEN was published in 1991 by the Department of Dermatology, University of Freiburg.[34] Case details were collected from hospitalized patients with SJS/TEN and SJS in West Germany from 1981 to 1985. Inquiries by telephone, letter, and personal visits produced an overall response rate of 91%. A total of 259 patients with TEN and 315 patients with SJS were identified. From these data, an overall annual risk of 0.93 per million for TEN and 1.1 per million for SJS were calculated.[34] As noted in the 1991 publication, this early report could not use the diagnostic ALDEN algorithm, which was published in 2010.[20]

Iran

A 2018 report from Iran announced an epidemiology study on SJS/TEN and provided interesting details about causative drugs, underlying diseases, duration of hospitalization, and types of treatment.[35] However, epidemiological data and cases assessed for causality using the diagnostic ALDEN algorithm published in 2010[20] were not provided.[35]

Italy

From northern Italy, the Lombardy Registry of Severe Cutaneous Reactions provided excellent incidence data on SJS/TEN in 2016.[36] Cases were assessed for causality using the ALDEN algorithm, as reported in 2010.[20] Data were collected from hospitals in the Lombardy region (9,502,272 people). A trained monitor visited the reporting hospitals to collect data on drug exposure and clinical features. Defined daily dose was used to express drug consumption. From April 2009 to November 2014, 17 cases of TEN and 59 cases of SJS were collected. Overall, the incidence rate was 1.40 cases (95% CI, 1.12–1.76) per million people per year, and 55.4% of the patients had a probable or very probable relation with drug exposure, based on the ALDEN score. In five patients (6.6%), no causative drug for the reaction was identifiable. Allopurinol contributed to the highest number of cases, with 23 patients, while the highest incidence was observed for cotrimoxazole (5.37 cases) and lamotrigine (3.54 cases) per 10 million defined daily dose/year.[36] The profile of drugs associated with the reactions was consistent with data from other surveillance systems.

Japan

In Japan, a nationwide epidemiology survey of SJS/TEN was carried out from 2016 to 2018, with expanded results published in 2008.[37] The study was primarily conceptualized by the Department of Dermatology, Showa University School of Medicine, Tokyo. A survey was sent to 1,205 institutions nationwide, which were asked to complete a postcard providing only the number of male and female SJS/TEN patients during the period. Without providing a population number considered in the study, the current yearly prevalence per million was estimated at 2.5 for SJS and 1 for TEN, based on local unscored diagnostic criteria.[37] However, verification of causality was not attempted using the validated ALDEN scoring algorithm, which is in common use worldwide as published in 2020.[20]

Korea

In Korea, a large population-based study in 2016 indicated that the overall annual incidence of SJS was 3.96 to 5.03 cases and of TEN 0.94 to 1.45 cases per million, using the National Health Insurance Database in Korea, considering a total population of 50,908,646.[38] The diagnostic codes L511 (SJS) and L512 (TEN) from the International Classification of Diseases-10th revision were used to define the target study population. However, the globally recognized ALDEN algorithm, published in 2010,[20] was not applied to verify the diagnoses.[38]

Saudi Arabia

A study from Saudi Arabia, published in 2020, analyzed the epidemiology of SJS/TEN at King Fahad Specialist Hospital in the Qassim region.[39] The retrospective study, which included only 10 patients, found an estimated incidence rate of SJS/TEN in the Qassim region to be 7.6 cases per million person-years.[39] However, no attempts were made to assess causality for the drug culprits using the diagnostic ALDEN algorithm, published 10 yearsearlier.[20]

Singapore

In Singapore, based on a small retrospective hospital-based study of 20 patients with TEN, the estimated annual incidence of TEN was 1.4 cases per million inhabitants.[28,42] However, a formal validated causality assessment method was not applied in the report published in 1995.[42]

Spain

In an analysis from Spain, conceptualized by the Clinical Pharmacology Unit at Príncipe de Asturias University Hospital in Alcalá de Henares, Madrid, incidences of SJS/TEN among new users of drugs were assessed.[41] The highest SJS/TEN incidence was found for phenytoin, with 68.9 per 100,000 new users, followed by dexamethasone with 5.48, and by allopurinol with 3.29.[41]

The United Kingdom (UK)

In the UK, the overall annual incidence of SJS/TEN was evaluated,[11,28] based on a large observational study on the epidemiology of SJS/TEN using data from the UK-based Clinical Practice Research Datalink.[11] Among 551 validated SJS/TEN patients, an incidence rate of 5.76 SJS/TEN cases per million person-years was calculated between 1995 and 2013. This rate was highest in patients aged one to ten

years and 80 years or older. This large, longitudinal observational study on the epidemiology of SJS/TEN contributes to the understanding of this still under-investigated severe skin disease in a European and white study population.[11] The incidence of TEN alone, due to all causes, was 0.5 per million person-years.

The USA

In the USA, the 1990 incidence of TEN due to all causes was 0.5 per million person-years, while for drug use, the incidence for SJS was 1.80 and for TEN was 9.0 per million person-years.[42] For this study, the clinical records of all patients who were hospitalized with these discharge diagnoses at Group Health Cooperative of Puget Sound in Seattle were reviewed from 1972 through 1986.[42] The diagnosis was based on record review and the application of a uniform set of diagnostic criteria, because the ALDEN score was only available 20 years later, in 2010.[32]

Similarly, another USA study, published in 2016, revealed the incidence of SJS/TEN hospitalizations, based on data from the 2009 to 2012 Nationwide Inpatient Sample, which contains a 20% sample of all USA hospitalizations.[43] Applying the International Classification of Disease, 9th edition, Clinical Modification codes, SJS, SJS/TEN overlap, and TEN were identified,[43] but not necessarily using the ALDEN scoring system from 2010,[32] which limits the quality of the presented data. The mean estimated incidences of SJS, SJS/TEN overlap, and TEN were 9.2, 1.6, and 1.9 per million adults per year.[43]

A more recent USA study in 2023 focused on the epidemiology of SJS/TEN but, in the text, described its objective as estimating the incidence of SJS/TEN limited to hospitalizations in the USA.[44] Accordingly, hospitalization data from the 2010 to 2020 National Inpatient Sample revealed a hospitalization rate of 73.0% for SJS alone, 15.3% for SJS/TEN overlap, and 14.0% for TEN alone. The ALDEN algorithm published in 2020[20] was not used in this 2023 USA study, and realistic epidemiology data, as promised in the title, were not provided.[44] Like the previous USA study of 2016.[43] the current report of 2023 shares the same database as the source, neglects to present real epidemiology data, and fails to apply the ALDEN algorithm.[44]

In the USA, current 2023 estimated incidences of SJS were 9.2, SJS/TEN overlap 1.6, and TEN 1.9 per million adults.[7,43,45] However, these figures must be viewed in light of the ignored application of the 2020 ALDEN algorithm to verify the diagnosis.[20]

Diagnostic challenges

Like any other complex disease, SJS/TEN and SJS/TEN overlap require a clear diagnosis, best achieved using the diagnostic ALDEN algorithm published in 2010.[20] The issue is that even recent articles published after 2010 on this complex disease failed to apply the ALDEN algorithm, and for reports published before 2010, no suitable tools were available. As a consequence, results often were not supported by validated causality assessment methods, making them vague and disputable. Additional diagnostic challenges focus on alternative dermatologic disorders, concomitant DILI that may confound the assumed clinical features of the complex disorders, the implicated culprit drugs, non-drug causes, and cases in which no culprit was found.

ALDEN-based SJS/TEN and SJS/TEN overlap

Cases evaluated by ALDEN with high causality gradings should be the preferred source for describing clinical features, instead of using those lacking the benefit of ALDEN. Uniformity in the future description of features and comparability among countries and regions can only be achieved by harmonizing diagnostic approaches. This goal is best accomplished by members of medical associations.

Differential dermatologic diseases

Known as a multifaceted disease, all three entities—SJS, SJS/TEN overlap, and TEN—require diagnostic verification by ALDEN, accompanied by a careful exclusion of differential diagnoses, with a primary focus on alternative dermatologic disorders. The exclusion of alternative dermatologic diseases must be handled by an experienced dermatologist to define the correct diagnosis and treatment option. Selected alternative dermatologic diseases are provided in a list (Table 1).[8–10,46–52]

Drugs implicated in RUCAM plus ALDEN based DILI associated with SJS/TEN

In SJS/TEN patients, abnormal LT, such as increased serum activities of ALT, AST, or ALP, were found.[5,19,53–56] To analyze this special cohort, patients with firm diagnoses of DILI as verified by RUCAM and SJS/TEN verified by ALDEN are preferred. DILI experts commonly apply RUCAM but occasionally forget to use ALDEN, which confounds the results. To provide an overview, selected cases are presented in a listing of suspected drugs in alphabetical order, along with whether an appropriate causality algorithm was applied (Table 2).[5,19,53–56]

It is encouraging to note that for this clinically important cohort, in five of six reports (83.3%), both RUCAM and ALDEN diagnostic algorithms were used together (Table 2).[5,19,54–56] This approach provided firm evidence for 203 cases that the suspected drugs were indeed the culprit medication. The listing also shows which drugs have a high risk of leading to death in patients (Table 2). The single study that applied RUCAM only and ignored the value of using ALDEN provided results not based on evidence (Table 2).[53] As a result, in SJS/TEN patients with suspected DILI, the use of both algorithms—RUCAM and ALDEN—should be obligatory in future studies and regarded as the primary gold standard.

Drugs as culprits in SJS/TEN verified by ALDEN only

The case data quality of a large cohort consisting of patients with ALDEN-based SJS/TEN was found to be appropriate, which allowed the attribution of a specific drug as the causative medication in 85% of patients.[20] For the remaining 15% of patients, a drug as the culprit could not be verified, classifying these cases as idiopathic. In two analytical reports, it was found that many drugs were causative in patients with SJS/TEN and high ALDEN scores.[20,57] While the combined use of the updated RUCAM with the ALDEN algorithm is the primary gold standard (Table 2), the use of the ALDEN scoring method alone is certainly the secondary gold standard, confined to cases lacking increased LTs and therefore not requiring the exclusion of DILI as an associated disorder for the diagnosis of SJS/TEN. Concomitantly, a significant number of drugs were identified for which causal attribution could not be verified. These data provide no evidence for erroneous claims that all drugs may trigger SJS/TEN.[20] For clinical purposes, a list of drugs is provided to indicate whether or not they cause SJS/TEN. Only cases assessed by ALDEN are included in the list (Table 3).[20,57]

Drugs implicated in merely suspected but not ascertained SJS/TEN

Other approaches focus on drugs assumed to be culprits of

Table 1. Dermatologic diseases as differential diagnoses of Stevens-Johnson syndrome/toxic epidermal necrolysis

Dermatology disease	Comments	References
Acute generalized exanthematous pustulosis	Nonfollicular, sterile pustules on an erythematous base	Frantz, 2021[8]; Szatkowski, 2015[46]
Acute or subacute cutaneous lupus with epidermal necrosis (Rowell syndrome)	Distinguishable by typical clinical and laboratory findings	Frantz, 2021[8]; Romero, 2018[47]
Bullous pemphigoid	ELISA testing. A biopsy for direct immunofluorescence: autoantibodies against the basement membrane zone	Frantz, 2021[8]; Baigrie, 2024[48]
Drug rashes	Commonly in the context of an allergy against a drug	Labib, 2024[9]
Erythema multiforme major	Considered the key differential diagnosis: <10% of BSA with symmetric acral distribution	Frantz, 2021[8]; Labib, 2024[9]
Exfoliative erythroderma	Usually painless and affects the skin only under sparing mucous membranes	Labib, 2024[9]
Generalized bullous fixed drug eruption, also termed: Generalized fixed drug eruption	Distinct by immunohistopatho-logical features	Frantz, 2021[8]; Cho, 2014[10]
Linear IgA bullous dermatosis	Autoimmune subepithelial vesiculobullous disease due to IgA autoantibodies directed against different antigens	Frantz, 2021[8]; Genovese, 2019[49]
Paraneoplastic pemphigus	A common mucocutaneous manifestation of malignancy	Frantz, 2021[8]; Labib, 2024[9]
Pemphigus vulgaris	Autoimmune disease that results in blisters on cutaneous and mucosal surfaces and is characterized primarily by acantholysis	Frantz, 2021[8]; Ingold, 2024[50]
Phototoxic eruptions	UVA-induced cutaneous photosensitive reactions	Frantz, 2021[8]; Glatz, 2012[51]
Staphylococcal scalded skin syndrome	Blistering of skin on superficial layers due to toxins released from *Staphylococcus aureus*	Frantz, 2021[8]; Mishra 2016[52]

BSA, body surface area; IgA, immunoglobulin A; UVA, ultraviolet A.

suspected SJS/TEN. In these reports, though often cited, the diagnosis was not verified by the ALDEN score, which regrettably makes the published data disputable and calls for caution regarding credibility.[7,58–72] Conditions were by no means improved when tools such as the Naranjo method, the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) method, the Liverpool method, or the Drug-Induced Liver Injury Network (DILIN) method were applied, alone or even in combination. These shortcomings apply to both single selected drugs and studies involving various drugs. To prevent misquotations, a selection of these disputable reports with selected drugs as examples in alphabetical order is presented in listing form (Table 4).[7,58–72]

Firm causality for drugs in SJS/TEN cannot confidently be achieved by any of these other listed tools, such as the Naranjo method, the WHO-UMC method, the Liverpool method, or the DILIN method (Table 4). In particular, they cannot replace the ALDEN algorithm for various reasons:[7,58–78] (1) The Naranjo method searches for any general adverse drug reaction in any organ or tissue.[73] It therefore lacks well-defined scoring elements specifically for SJS/TEN.[58,65,66,69–72] Its reliability has been questioned by a number of investigators,[22,65,74] particularly regarding its specificity in cases of DILI and HILI.[22,74,75] (2) Similar issues apply to the Liverpool method.[65] which integrates the Naranjo method.[22,65] (3) A common feature of the WHO-UMC method[76] and the Naranjo method[73] is that both are general causality tools for any adverse drug reaction, without considering the specifics of disease such as SJS/TEN[68,70–72] or cases of DILI or HILI.[22,74–77] (4) The DILIN method is not designed to consider SJS/TEN specifics[67] and lacks validation features based on the so-called global introspection approach, which involves subjective opinions and outputs poor quality data, making the results highly questionable.[78] (5) In addition to the few selected drugs presented as examples (Table 4), the scientific literature provides several hundred similar drugs evaluated using non-ALDEN approaches that should not be quoted in publications. (6) A study examining the agreement among four different causality-assessing tools for cases of drug-induced SJS, TEN, and SJS/TEN overlap[79] found poor reproducibility and varying levels of agreement among the different causality assessment tools,[72] Overall, alternative tools to the ALDEN algorithm are outdated and cannot be applied to assess causality for drugs in SJS/TEN cases.

As opposed to drugs implicated in merely suspected but not ascertained SJS/TEN cases (Table 4), individual culprit drugs are better retrieved from studies that analyzed cases assessed by RUCAM combined with ALDEN (Table 2)[5,19,53–56] or by ALDEN alone (Table 3).[20,57] A thorough review of variable detailed case reports published over four decades from 1980 to 2020 identified, in 957/1,059 cases (90.4%) with probable or definite causality grading, a large number of conventional drugs as culprits.[7] However, these figures provide only a rough estimate, since individual methods to assess causality were not integrated into the analysis as rarely provided by the evaluated case reports. Overall, 379 drug culprits were reported; the most frequently reported drugs were antibiotics (n = 285, 26.9%), followed by anticonvulsants (n = 196, 18.5%), analgesics/anesthetics (n = 126, 11.9%), and antineoplastics (n = 120, 11.3%).[7]

Non-drug culprits as differential diagnoses

ALDEN-based studies identified culprit drugs in 85% of SJS/

Table 2. Selected drugs implicated in RUCAM based DILI and ALDEN based SJS/TEN

Drugs/drug classes	Cases (n)	Causality algorithm	Outcome	References
Allopurinol	2	RUCAM + ALDEN +	All survived	Devarbhavi, 2016[5]
Allopurinol	1	RUCAM + ALDEN +	N.A.	Zhang, 2020[19]
Amoxicillin	N.A.	RUCAM + ALDEN −	Cases of acute liver failure	Ortega-Alonso, 2017[53]
Ampicillin	N.A.	RUCAM + ALDEN −	Cases of acute liver failure	Ortega-Alonso, 2017[53]
Aspirin	1	RUCAM + ALDEN +	N.A.	Zhang, 2020[19]
Carbamazepine	2	RUCAM + ALDEN +	All died	Devarbhavi, 2016[5]
Carbamazepine	8	RUCAM + ALDEN +	N.A.	Zhang, 2020[19]
Carbamazepine	36	RUCAM + ALDEN +	4/36 died	Devarbhavi, 2023[54]
Ceftazidime	1	RUCAM + ALDEN +	N.A.	Zhang, 2020[19]
Ceftriaxone	1	RUCAM + ALDEN +	Lethal outcome	Devarbhavi, 2016[5]
Ceftriaxone	1	RUCAM + ALDEN +	N.A.	Zhang, 2020[19]
Celecoxib	N.A.	RUCAM + ALDEN −	No cases of acute liver failure	Ortega-Alonso, 2017[53]
Clobazam	2	RUCAM + ALDEN +	1/3 died	Devarbhavi, 2023[54]
Clonazepam	2	RUCAM + ALDEN +	All survived	Devarbhavi, 2023[54]
Cotrimoxazole	3	RUCAM + ALDEN +	All survived	Devarbhavi, 2016[5]
Dapsone	5	RUCAM + ALDEN +	3/5 died	Devarbhavi, 2016[5]
Fluoxetine	1	RUCAM + ALDEN +	Survived	Agrawal, 2019[55]
Gabapentin	1	RUCAM + ALDEN +	Survived	Devarbhavi, 2023[54]
Ibuprofen	N.A.	RUCAM + ALDEN −	Cases of acute liver failure	Ortega-Alonso, 2017[53]
Lamotrigine	1	RUCAM + ALDEN +	Lethal outcome	Devarbhavi, 2016[5]
Lamotrigine	1	RUCAM + ALDEN +	N.A.	Zhang, 2020[19]
Lamotrigine	3	RUCAM + ALDEN +	1/3 died	Devarbhavi, 2023[54]
Leflunomide	3	RUCAM + ALDEN +	All died	Devarbhavi, 2016[5]
Leflunomide	2	RUCAM + ALDEN +	N.A.	Zhang, 2020[19]
Levitericetam	1	RUCAM + ALDEN +	Lethal outcome	Devarbhavi, 2016[5]
Levitericetam	3	RUCAM + ALDEN +	All survived	Devarbhavi, 2023[54]
Levofloxacin	1	RUCAM + ALDEN +	Survived	Devarbhavi, 2016[5]

(continued)

Table 2. *(continued)*

Drugs/drug classes	Cases (n)	Causality algorithm	Outcome	References
Nevirapine	6	RUCAM + ALDEN +	All survived	Devarbhavi, 2016[5]
Omeprazole	1	RUCAM + ALDEN +	N.A.	Zhang, 2020[19]
Oxacarbazepine	1	RUCAM + ALDEN +	Survived	Devarbhavi, 2016[5]
Oxacarbazepine	2	RUCAM + ALDEN +	N.A.	Zhang, 2020[19]
Oxacarbazepine	2	RUCAM + ALDEN +	All survived	Devarbhavi, 2023[54]
Paracetamol	1	RUCAM + ALDEN +	N.A.	Zhang, 2020[19]
Penicillin	1	RUCAM + ALDEN +	N.A.	Zhang, 2020[19]
Phenobarbitone	2	RUCAM + ALDEN	1/2 died	Devarbhavi, 2016[5]
Phenobarbitone	1	RUCAM + ALDEN +	N.A.	Zhang, 2020[19]
Phenobarbitone	8	RUCAM + ALDEN +	2/8 died	Devarbhavi, 2023[54]
Phenylbutazone	2	RUCAM + ALDEN +	N.A.	Zhang, 2020[19]
Phenytoin	2	RUCAM + ALDEN +	1/2 died	Devarbhavi, 2016[5]
Phenytoin	1	RUCAM + ALDEN +	N.A.	Zhang, 2020[19]
Phenytoin	71	RUCAM + ALDEN +	4/71 died	Devarbhavi 2023[54]
Tegafur	1	RUCAM + ALDEN +	N.A.	Zhang, 2020[19]
Terbinafine	N.A.	RUCAM + ALDEN −	Cases of acute liver failure	Ortega-Alonso, 2017[53]
Topiramate	1	RUCAM + ALDEN +	Survived	Devarbhavi, 2023[54]
Valproate	14	RUCAM + ALDEN +	1/14 died	Devarbhavi, 2023[54]
Warfarin	1	RUCAM + ALDEN +	Survived	Xiong 2021[56]
Zonisamide	1	RUCAM + ALDEN +	Survived	Devarbhavi, 2023[54]

This table compiles selected drugs implicated in causing DILI in patients with SJS/TEN. For all listed drugs, the causality of DILI for the culprit drug was verified using the RUCAM algorithm, and for most drugs, the diagnosis of SJS/TEN was verified using the ALDEN algorithm. The listing is confined to conventional drugs, excluding herbal medicines like herbal TCM, because these non-drugs cause herb-induced liver injury rather than DILI. The "+" sign indicates that the specific diagnostic algorithm was used to verify the diagnosis, whereas the "–" sign indicates that the specific algorithm was not applied. RUCAM, Roussel Uclaf Causality Assessment Method; DILI, drug-induced liver injury; ALDEN, Algorithm of Drug Causality for Epidermal Necrolysis; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; N.A., not available; TCM, traditional Chinese Medicines.

TEN cases[29] and in 88.6%,[20] a figure similar to the 90.4% found in the non-ALDEN study discussed above.[7] Valid estimates of the contribution by non-drugs to the disease are difficult to obtain, as this topic was rarely addressed in the reports. Crude figures are likely between 10% and 19%.[7,20,30] Among all SJS/TEN cases, infections were the most common non-drug causes, with Mycoplasma infections being the most common, followed by radiotherapy.[7] In another study, though without using the ALDEN or RUCAM algorithms to verify causality, drug-related culprits accounted for 52.4% and non-drug culprits for 47.6% of all SJS/TEN cases.[7] Results of non-drug causatives provided by reports are presented in a separate listing (Table 5).[7,14,30,80–85]

Unidentified culprits

For a small group in each SJS/TEN cohort, after ruling out overt causes related to drug use (Tables 2 and 3) or exposure to non-drugs (Table 5), robust culprits may not be easily detectable, as evidenced by the lack of respective information in all SJS/TEN publications of case reports or case series. A

Table 3. Drugs implicated or not implicated in SJS or TEN as verified by ALDEN

Drugs/drug classes	Cases (n)	Diagnostic causality algorithm	References
ACE inhibitors	0	ALDEN +	Sassolas, 2020[20]
Acetylsalicylic acid	0	ALDEN +	Sassolas, 2010[20]
Acetaminophen	8	ALDEN +	Sassolas, 2010[20]
Allopurinol	5	ALDEN +	Sassolas, 2010[20]
Allopurinol	11	ALDEN +	Gronich, 2022[57]
Amoxicillin	6	ALDEN +	Gronich, 2022[57]
Amoxicillin-clavulanate	4	ALDEN +	Gronich, 2022[57]
Aciclovir	1	ALDEN +	Gronich, 2022[57]
Bendamustine	2	ALDEN +	Gronich, 2022[57]
Benzodiazepines	0	ALDEN +	Sassolas, 2010[20]
Beta-blockers	0	ALDEN +	Sassolas, 2010[20]
Calcium channel blockers	0	ALDEN +	Sassolas, 2010[20]
Cabozantinib	1	ALDEN +	Gronich, 2022[57]
Carbamazepine	2	ALDEN +	Gronich, 2022[57]
Carfilzomib	1	ALDEN +	Gronich, 2022[57]
Cefazolin	1	ALDEN +	Gronich, 2022[57]
Ceftriaxone	1	ALDEN +	Gronich, 2022[57]
Cefuroxime	4	ALDEN +	Gronich, 2022[57]
Celecoxib	1	ALDEN +	Gronich, 2022[57]
Ciprofloxacin	6	ALDEN +	Gronich, 2022[57]
Citalopram	1	ALDEN +	Sassolas, 2010[20]
Citalopram	1	ALDEN +	Gronich, 2022[57]
Clindamycin	4	ALDEN +	Gronich, 2022[57]
Codeine	1	ALDEN +	Gronich, 2022[57]
Corticosteroids	7	ALDEN +	Sassolas, 2010[20]
Dipyrone	3	ALDEN +	Gronich, 2022[57]
Etodolac	3	ALDEN +	Gronich, 2022[57]
Etoricoxib	5	ALDEN +	Gronich, 2022[57]
Fluconazole	2	ALDEN +	Sassolas, 2010[20]
Fluoxetine	2	ALDEN +	Sassolas, 2010[20]
H1 anti-histamine	0	ALDEN +	Sassolas, 2010[20]
HMG-CoA reductases, statins	0	ALDEN	Sassolas, 2010[20]
Hydrochloroquine	1	ALDEN +	Gronich, 2022[57]
Ibuprofen	0	ALDEN +	Sassolas, 2010[20]
Ibuprofen	1	ALDEN +	Gronich, 2022[57]
Ketoprofen	3	ALDEN +	Sassolas, 2010[20]
Lamotrigine	1	ALDEN +	Sassolas, 2010[20]
Lamotrigine	9	ALDEN +	Gronich, 2022[57]
Levomepromazine	1	ALDEN +	Gronich, 2022[57]
Macrogol	1	ALDEN +	Gronich, 2022[57]
Leflunomide	1	ALDEN +	Sassolas, 2010[20]
Metamizole	2	ALDEN +	Sassolas, 2010[20]
Metronidazole	1	ALDEN +	Sassolas, 2010[20]

(continued)

Table 3. *(continued)*

Drugs/drug classes	Cases (n)	Diagnostic causality algorithm	References
Naproxen	1	ALDEN +	Sassolas, 2010[20]
Nimesulide	1	ALDEN +	Sassolas, 2010[20]
Nitrates	0	ALDEN +	Sassolas, 2020[20]
Nitrofurantoin	1	ALDEN +	Gronich, 2022[57]
Ofloxacin	1	ALDEN +	Gronich, 2022[57]
Paroxetine	1	ALDEN +	Sassolas, 2010[20]
Phenylbutazone	1	ALDEN +	Sassolas, 2010[20]
Phenylbutazone and kebuzone	3	ALDEN +	Sassolas, 2010[20]
Phenytoin	1	ALDEN +	Sassolas, 2010[20]
Phenytoin	8	ALDEN +	Gronich, 2022[57]
Pralatrexate	1	ALDEN +	Gronich, 2022[57]
Pregabalin	1	ALDEN +	Gronich, 2022[57]
Pyrazolone analgesics	6	ALDEN +	Sassolas, 2010[20]
Quetiapine	1	ALDEN +	Gronich, 2022[57]
Roxithromycin	3	ALDEN +	Gronich, 2022[57]
Spironolactone	0	ALDEN +	Sassolas, 2010[20]
Sulfamethoxazole	1	ALDEN +	Sassolas, 2010[20]
Sulfasalazine	1	ALDEN +	Gronich, 2022[57]
Sulfonylurea antidiabetics	0	ALDEN +	Sassolas, 2010[20]
Sunitinib	1	ALDEN+	Gronich, 2022[57]
Terbinafine	1	ALDEN +	Gronich, 2022[57]
Thiabendazole	2	ALDEN +	Sassolas, 2010[20]
Thiazide diuretics	0	ALDEN +	Sassolas, 2010[20]
Thioacetazone	1	ALDEN +	Sassolas, 2010[20]
Topiramate	1	ALDEN +	Gronich, 2022[57]
Tramadol	0	ALDEN +	Sassolas, 2010[20]
Trimethoprim-sulfamethoxazole	4	ALDEN +	Gronich, 2022[57]
Vancomycin	3	ALDEN +	Gronich, 2022[57]
Valproic acid	3	ALDEN +	Sassolas, 2010[20]
Valproic acid	4	ALDEN +	Gronich, 2022[57]
Vasodilators	0	ALDEN +	Sassolas, 2010[20]

This listing provides good evidence for various drugs causing ALDEN-based SJS/TEN, but also for other drugs that do not cause SJS/TEN. The "+" sign indicates that the specific diagnostic algorithm was used to verify the diagnosis, whereas the "–" sign indicates that the specific algorithm was not applied. SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; ALDEN, Algorithm of Drug Causality for Epidermal Necrolysis.

few reports have addressed this issue, and agreement exists that 5–35% of cases remain idiopathic.[15,20,66,86] Many tests are warranted to identify the cause of SJS. If all of them are performed, it may be possible to clarify the etiology of SJS, which would otherwise be classified as idiopathic.[82] An overview of reports dealing with unidentified causes in SJS/TEN is given in a listing (Table 6).[15,20,29,36,66,82,86–88]

Diagnosis of skin lesions

SJS/TEN may affect various organs and requires a multidisciplinary approach for diagnostic purposes. The diagnostic, clinical, and therapeutic management of patients with suspected SJS/TEN starts with examining the skin, which should show a positive Nikolsky sign.[89] When tested, the very thin top layer of skin will shear off when rubbed, leaving the skin pink, moist, and usually very tender. SJS/TEN is characterized by a macular exanthema ('atypical targets') which focuses on the face, neck, and central trunk regions. Lesions show rapid confluence, quickly resulting in widespread epidermal detachment and erosions. Other dermatologic disorders must be excluded (Table 1), and causality assessment for drugs must be initiated by using the ALDEN algorithm in all patients with recent drug treatment.[20] Whenever increased LTs are found and drugs were recently used, the updated RUCAM must be applied to evaluate whether DILI is part of the SJS/TEN diagnosis.[22]

Table 4. Drugs implicated in Stevens-Johnson syndrome or toxic epidermal necrolysis suspected mostly by non-ALDEN tools

Drugs/ drug classes	Cases (n)	Diagnostic causality algorithm	Selected drugs with details and comments	References
Amoxicillin-Clavulanate	1	Naranjo + ALDEN –	Lethal outcome	Limauro, 1999[58]
Cephradine	1	None ALDEN –	Acetaminophen as comedication	Nam, 2011[59]
Ibuprofen	1	None ALDEN –	Stevens-Johnson syndrome associated with liver injury	Gui, 2021[60]
Paracetamol	1	None ALDEN –	Paracetamol was used in therapeutic dose	Slim, 2015[61]
Paracetamol	1	None ALDEN –	Comedication with Cefdinir	Totsuka, 2021[62]
Various drugs	123	None ALDEN –	Acetylsalicylic acid Barbiturates Diphenylhydantoin Phenylbutazone	Nethercott, 1985[63]
Various drugs	1	None ALDEN –	Clonidine Ferrous sulfate Nifedipine	Cheryan, 1995[64]
Various drugs	80	Naranjo + Liverpool + ALDEN –	N.A.	Gallagher, 2011[65]
Various drugs	29	Naranjo + ALDEN –	Antibiotics Antiepileptics Antiinflammatory drugs Antirheumatic drugs	Bang, 2012[66]
Various drugs	4	DILIN + ALDEN –	Azithromycin Lamotrigine	Chalasani, 2015[67]
Various drugs	88	WHO-UMC + ALDEN –	Antibiotics Anticonvulsants	Wang, 2017[68]
Various drugs	10	Naranjo + Liverpool + ALDEN +	N.A.	Goldman, 2019[69]
Various drugs	158	Naranjo + WHO-UMC + ALDEN –	Antimicrobials NSAIDS	James, 2022[70]
Various drugs	19	Naranjo + WHO-UMC + ALDEN –	Aceclofenac Ampicillin Anacin Carbamazepine	Kanagarajan, 2023[71]
Various drugs	30	Liverpool + Naranjo + WHO-UMC + ALDEN +	Anticonvulsants Antimicrobials NSAIDS	Sivagourounadin, 2022[72]
Various drugs	1,059	None specified	Phenytoin Trimethoprim-sulfamethoxazole	Wang, 2022[7]

The "+" sign indicates that the specific diagnostic algorithm was used to verify the diagnosis, whereas the "–" sign indicates that the specific algorithm was not applied. ALDEN, Algorithm of Drug Causality for Epidermal Necrolysis; DILIN, Drug-Induced Liver Injury Network; N.A., not available; NSAIDS, nonsteroidal anti-inflammatory drugs; WHO-UMC, World Health Organization-Uppsala Monitoring Centre.

SJS/TEN types 1–5

SJS/TEN is a rare, serious disorder primarily affecting the skin and mucous membranes, with characteristic features common to all its varieties.[6] Known as a clinical challenge, SJS/TEN represents a heterogeneous cohort characterized by several categories. These categories reflect the diversity of clinical features in SJS/TEN patients, considering the type of culprits causing the SJS/TEN and DILI disease. Accordingly, several SJS/TEN categories must be differentiated: (1) The best-studied cohort consists of SJS/TEN patients with conventional drugs as culprits, assessed for causality using both the RUCAM and ALDEN diagnostic algorithms (Table 2).[5,19,53–56] For this cohort, the diagnosis of DILI and SJS/TEN is well established and classified as SJS/TEN type 1. (2) The second cohort consists of drugs that cause SJS/TEN, with diagnosis verified by using the ALDEN algorithm (Table 3).[20,57] This cohort is classified as SJS/TEN type 2. (3) The third cohort comprises drugs that cause SJS or TEN, suspected by non-

Table 5. Non-drug culprits implicated in causing SJS, TEN, or SJS/TEN overlap

Non-drug culprit	Cases (n)	Comments	References
Acetochlor	1	Industrial chemical	Yang, 2018[30]
Arsenic	1	Heavy metal	Yang, 2018[30]
Biological	2	Vaccine	Wang, 2022[7]
Carbamate	1	Occupational exposure to this insecticide	Lim, 2010[80]
Cardiac catheterization dye	1	Not further specified	Wang, 2022[7]
Chemical substance	10	Arsenic (2x) Dimethyl cyanocarbonimido-dithionate (1x) Carbamate insecticide (2x) Gangliosides (1x) Iodine (1x) Mercury (1x) Organophosphate insecticide (1x) Trichloroethylene (1x)	Wang, 2022[7]
Chinese patent medicines	18	Not specified	Wang, 2022[7]
Contrast medium as diagnostic	9	Not further specified	Wang, 2022[7]
Coxsackie virus A6	8	Identified as CVA 6 in blistering skin lesions (6x) and isolated by a throat swab (2x)	Chung, 2013[81]
Diatrizoate meglumine-diatrizoate sodium	1	Known as Gastrografin, used for oral radiographic examination of esophagus, stomach, proximal small intestine, and colon	Wang, 2022[7]
Enterovirus	1	Acquired in a stable	De Guido, 2020[82]
Glyphosate	1	Following inhalation of this herbicide, short treatment with aspirin, paracetamol, and chlorpheniramine	Voltan, 2010[83]
Hair dry	1	Not specified	Kim, 2012[84]
Hepatitis A	1	Hepatitis A virus (HAV) was assumed by error as cause of cirrhosis. However, acute HAV never causes chronic liver disease like incipient cirrhosis	Zang, 2023[85]
Herbal medicines	44 5	Not further specified Not further specified	Wang, 2022[7] Kim, 2012[84]
Herbal medicines	7	Ayurvedic medicines (3x) Golden health blood purifying tablets (1x) Moringa oleifera (1x) Ophiopogonis tuber (1x) Traditional Chinese Medicines (1x)	Wang, 2022[7]
Infections	25	Brucella melitensis (1x) Cytomegalovirus infection (1x) Dengue virus (1x) Enterovirus (1x) Epstein-Barr virus infection (1x) Herpes simplex virus (4x) Influenza B infection (2x) Mucor infection (1x) Parvovirus infection (1x) Pneumonia infection (1x) Psittacosis (1x) Respiratory infection (2x) Staphylococcus septicemia (1x) Upper respiratory infection (1x) Varicella infection (1x) Varicella-zoster virus (1x) Viral hepatitis A (1x) Viral illness (2x) Yersinia enterocolica infection (1x)	Wang, 2022[7]

(continued)

Table 5. *(continued)*

Non-drug culprit	Cases (n)	Comments	References
Mycoplasma pneumonia infection	44	Highest frequency in SJS patients	Wang, 2022[7]
Naphthalenedisulfonic acid dimethyl ester	1	Industrial chemical	Yang, 2018[30]
Others	25	Various diseases and other causes specified	Wang, 2022[7]
Others	39	Not specified	Kim, 2012[84]
Radiotherapy	29	Brain radiotherapy (15x) Unspecified radiotherapy (1x) and associated with drug use in 20 patients	Wang, 2022[7]
Trichloroethylene	1	Industrial chemical	Yang, 2018[30]
Vaccines	9	Vaccine against: Anthrax (1x) Hanta virus (1x) Measles (1x) MPR (1x) Rabies (1x) Small pox (1x) Tetanus (1x) Varicella zoster virus (1x) Yellow fever (1x)	Wang, 2022[7]
Vitamins	3	Pyritinol (1x) Supradyn (1x) Vitamin B complex (1x)	Wang, 2022[7]
Ultraviolet radiation	13	Combined with these drugs: Carbamazepine (1x) Chloroquine (1x) Ciprofloxacin (1x) Hydroxychloroquine (3x) Ibuprofen (1x) Itraconazole (1x) Lamotrigine (2x) Naproxene (1x) Sulfasalazine (1x) Tramadol (1x)	McKinley, 2023[14]

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; MPR, measles, parotitis, and rubella.

ALDEN tools (Table 4),[7,58–72] and is now classified as SJS/TEN type 3. (4) The fourth cohort consists of patients with SJS/TEN caused by non-drugs (Table 5)[7,14,30,80–85] and is classified as SJS/TEN type 4. (5) The fifth cohort combines patients with SJS/TEN caused by unidentified culprits (Table 6)[15,20,29,36,66,82,87,88] and is classified as SJS/TEN type 5. For a quick overview, the SJS/TEN categories are lister (Table 7).[5,7,14,15,19,20,30,36,53–72,81–85,87,88]

Table 6. Unidentified culprits in SJS/TEN

References	SJS, TEN alone, or together	Cases (n)	Diagnostic causality algorithm	Details and comments
Zimmerman, 2019[15] Wolff, 2012[86]	SJS/TEN	N.A.	N.A.	Discussed is the fact that 5–20% of cases remain idiopathic
Sassolas, 2010[20]	SJS TEN	N.A.	ALDEN	In 65% of SJS and TEN, drugs were implicated as opposed to 35% with non-drug unidentified culprits
Diphoorn, 2016[36]	SJS/TEN	76	ALDEN	No drug a causative was found in 6.6% of cases
Bang, 2012[66]	SJS	N.A.	SCORTEN Naranjo	More than 80% of SJS were caused by drugs and 20% by non-drug unidentified culprits
De Guido, 2020[82]	SJS	N.A.	N.A.	Discussed is the role of drugs in 53–95% of cases, of infections in 5–31%, and idiopathic in 5–18%
Nozaki, 2015[87]	SJS	8	SCORTEN	Therapy study was done in all non-drug cases
Shanbhag, 2020[88]	SJS/TEN	N.A.	N.A.	Mentioned is the fact that no drug origin could be identified in 15% of cases
Cheung, 2024[29]	SJS/TEN	124	ALDEN	No cause was identified in 4.8% of cases

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; N.A., not available; ALDEN, Algorithm of Drug Causality for Epidermal Necrolysis; SCORTEN, severity-of-illness score for toxic epidermal necrolysis.

Table 7. SJS/TEN categories

SJS/TEN Category	Definition	Details
SJS/TEN Type 1	Drugs cause drug-induced liver injury to be assessed by RUCAM and SJS/TEN assessed by ALDEN. Exhaustive information at: Devarbhavi, 2016;[5] Zhang, 2020;[19] Ortega-Alonso, 2016;[53] Devarbhavi, 2023;[54] Agrawal, 2019;[55] Xiong, 2021.[56]	Table 2
SJS/TEN Type 2	Drugs cause SJS/TEN to be assessed by ALDEN. Exhaustive information at: Sassolas, 2010;[20] Gronich, 2022.[57]	Table 3
SJS/TEN Type 3	Drugs may cause SJS/TEN to be assessed by non-RUCAM and non-ALDEN tools Exhaustive information at: Wang, 2022;[7] Limauro, 1999;[58] Nam, 2011;[59] Gui, 2021;[60] Slim, 2015;[61] Totsuka, 2021;[62] Nethercott, 1985;[63] Cheriyan, 1995;[64] Gallagher, 2011;[65] Bang, 2012;[66] Chalasani, 2015;[67] Wang, 2017;[68] Goldman, 2019;[69] James, 2022;[70] Kanagarajan, 2023;[71] Sivagourounadin, 2023.[72]	Table 4
SJS/TEN Type 4	Non-drugs cause SJS/TEN to be assessed by various tools. Exhaustive information at: Wang, 2022;[7] Garg, 2023;[14] Yang, 2018;[30] Lim, 2010;[80] Chung, 2013;[81]De Guido, 2020;[82] Voltan, 2010;[83] Kim, 2012;[84] Zang, 2022.[85]	Table 5
SJS/TEN Type 5	Unknown culprits cause SJS/TEN to be assessed by various tools. Exhaustive information at: Zimmerman, 2019;[15] Sassolas, 2010;[20] Diphoorn, 2016;[36] Bang, 2012;[66] De Guido, 2022;[82] Nozaki, 2015;[87] Shanbhag, 2022.[88]	Table 6

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; RUCAM, Roussel Uclaf Causality Assessment Method; ALDEN, Algorithm of Drug Causality for Epidermal Necrolysis.

Differential diagnoses

Diagnostic work-up of increased liver tests

Increased LTs and DILI are often recognized in SJS/TEN patients (Table 2). According to a large retrospective SCORTEN-based study, DILI (64/213, 30.0%) was among the most common complications.[90] However, not all abnormal LTs can be ascribed to RUCAM-based DILI, which requires additional efforts to search for other liver diseases.

In any patient with suspected liver injury, a firm diagnosis of the drug implicated in the liver injury is needed for an adequate evaluation of the case. Increased LTs signify the presence of liver injury but do not provide information about its cause, as they can be found in other hepatic, extrahepatic, and systemic diseases. Consequently, alternative causes may confound the DILI diagnosis.

Exclusion of alternative causes in DILI

Special attention is needed to exclude competing causes (Table 8).[22]

Clinical features

Symptoms

Reported symptoms of SJS/TEN are multifaceted, related to the stage of the disease and the number of organs involved. A careful review of the symptoms most commonly observed has been reported.[79] SJS/TEN is characterized by painful blisters, purpuric macules, and atypical target lesions with both skin and mucosal involvement. Lesions typically begin to appear four to twenty-eight days after the start of the culprit drug intake. The skin rash is often preceded by malaise, fever, and upper respiratory tract involvement with flu-like symptoms. SJS/TEN patients commonly have mucosal alterations of the eyes, mouth, and genitalia. In addition to the skin and mucosal involvement of special organs, other organ systems, such as the cardiovascular, pulmonary, gastrointestinal, and urinary tract systems, may also be affected, some of which are also classified as mucosal involvement. Multiple organ involvement may cause complications and sequelae. Skin infections, pneumonia, hepatitis, and sepsis are frequently reported complications of SJS/TEN, which may result in mortality.[79] For individual drugs causing SJS/TEN, symptoms are well described in case reports evaluated by RUCAM and ALDEN, belonging to the SJS/TEN type 1 group (Table 2). In this context, clinical features were described from China in a study of 298 SJS/TEN patients[19] with SJS/TEN type 1 (Table 7). Among them, 40 patients (13.42%) had liver injury, with the main clinical manifestations including yellow staining of the skin and sclera (11 patients; 27.5%), skin itching (24 patients; 60%), yellow coloration of the urine (11 patients; 27.5%), liver discomfort (six patients; 15%), fatigue (10 patients; 25%), inappetence (11 patients; 27.5%), fever (35 patients; 87.25%), and mucosal rash (23 patients; 57.5%). Half of the 40 patients received a highly probable RUCAM-based causality grading, while the other half achieved a probable grading, substantiating the overall high study quality.[19] However, the clinical manifestations of the 258 non-DILI patients (86.58%) were not presented in this study.

Laboratory data

In a study of 11 SJS/TEN patients, two patients had lymphopenia (<2,000/mm^3), three patients had anemia (<12 g/dL), five patients had slightly increased ALT and/or AST levels (>40 U/L, <100 U/L), seven patients had increased C-reactive protein levels (>0.5 mg/dL), two patients had slightly decreased sodium levels (130–135 mEq/L) and decreased potassium levels (<3.5 mEq/L), three patients had decreased albumin levels (<3.5 g/dL), and one patient had hypogammaglobulinemia at the time of presentation.[91]

Blood eosinophilia is not a characteristic feature of SJS/TEN but is more commonly seen in the context of the drug reaction eosinophilia and systemic symptoms (DRESS) syndrome, also known as drug-induced hypersensitivity syndrome (DIHS).[92,93] This special disease entity is characterized by cutaneous eruptions, fever, and multiorgan involvement with a preference for the liver.[93]

Skin histology

Skin biopsies taken from 13 SJS/TEN patients revealed variable histopathological features.[94] These included epidermal necrosis (eight patients), basal vacuolar changes (10 patients), and subepidermal bullae (10 patients). Biopsy specimens from 11 patients displayed moderate or dense dermal

Table 8. Possible alternative causes of increased liver tests apart from DILI

Differential diagnosis	Diagnostic parameters
HAV	Anti-HAV-IgM
HBV	HBV-DNA, anti-HBc-IgM
HCV	HCV-RNA, anti-HCV
HEV	HEV-RNA, titer change for anti-HEV-IgM/anti-HEV-IgG
CMV	CMV-PCR, titer change for anti-CMV-IgM/anti-CMV-IgG
EBV	EBV-PCR, titer change for anti-EBV-IgM/anti-EBV-IgG
HSV	HSV-PCR, titer change for anti-HSV-IgM/anti-HSV- IgG
VZV	VZV-PCR, titer change for anti-VZV-IgM/anti-VZV- IgG
Other viral infections according to the clinical context	Specific serology of Adenovirus, Coxsackie-B-Virus, Echovirus, Measles virus, Rubella virus, Flavivirus, Arenavirus, Filovirus, Parvovirus, HIV, and others
Other infectious diseases	Specific assessment of bacteria, fungi, parasites, and others
Herb induced liver injury	Updated RUCAM
AIH type I	Gamma globulins, ANA, SMA, AAA, SLA/LP, Anti-LSP, Anti-ASGPR
AIH type II	Gamma globulins, Anti-LKM-1 (CYP 2D6), Anti-LKM-2 (CYP 2C9), Anti-LKM-3
PBC	AMA, Anti-PDH-E2
PSC	p-ANCA, MRC
AIC	ANA, SMA
Overlap syndromes	See AIH, PBC, PSC, and AIC
Metabolic dysfunction-associated steatotic liver disease	BMI, insulin resistance, hepatomegaly, echogenicity of the liver
Alcoholic liver disease	Patient's history, clinical and laboratory assessment, other features of alcoholic disease
Cocaine, ecstasy and other amphetamines	Toxin screening
Rare intoxications	Toxin screening for household and occupational toxins
Hemochromatosis	Serum ferritin, total iron-binding capacity, genotyping for C2824 and H63D mutation, hepatic iron content
Wilson disease	Copper excretion (24 h urine), ceruloplasmin in serum, free copper in serum, Coombs-negative hemolytic anemia, hepatic copper content, Kayser-Fleischer-ring, neurologic-psychiatric work-up, genotyping. Modified Leipzig Scoring System for Wilson disease
Porphyria	Porphobilinogen in urine, total porphyrins in urine
α_1-Antitrypsin deficiency	α_1-Antitrypsin in serum
Biliary diseases	Clinical and laboratory assessment, hepatobiliary sonography, and other imaging (CT, MRC)
Pancreatic diseases	Clinical and laboratory assessment, sonography, CT, MRT
Celiac disease	TTG antibodies, endomysium antibodies, duodenal biopsy
Anorexia nervosa	Clinical context
Parenteral nutrition	Clinical context
Cardiopulmonary diseases	Cardiopulmonary assessment of congestive heart disease, myocardial infarction, cardiomyopathy, cardiac valvular dysfunction, pulmonary embolism, pericardial diseases, arrhythmia, hemorrhagic shock, and various other conditions
Addison disease	Plasma cortisol
Thyroid diseases	TSH basal, T4, T3
Grand mal seizures	Clinical context of epileptic seizure (duration >30 min)
Heat stroke	Shock, hyperthermia
Polytrauma	Shock, liver injury
Systemic diseases	Specific assessment of sarcoidosis, amyloidosis, metastatic tumor, sepsis, and others
Other diseases	Clinical context

This listing compilation is adapted and derived from a previous open-access publication. Although not comprehensive, it is to be used as a guide for patients with suspected liver injury.[22] AAA, anti-actin antibodies; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; ASGPR, asialo-glycoprotein receptor; BMI, body mass index; CT, computed tomography; CYP, cytochrome P450; PDH, Pyruvate dehydrogenase; HAV, hepatitis A virus; HBc, hepatitis B core; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; VZV, varicella zoster virus; HIV; human immunodeficiency virus; AIH, autoimmune hepatitis; LKM, liver kidney microsomes; LP, liver-pancreas antigen; LSP, liver-specific protein; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; MRC, magnetic resonance cholangiography; AIC, autoimmune cholangitis; MRT, Magnetic resonance tomography; p-ANCA, perinuclear antineutrophil; RUCAM, Roussel Uclaf Causality Assessment Method; SLA, soluble liver antigen; SMA, smooth muscle antibodies; TSH, thyroid stimulating hormone.

infiltrates. Histologic features in drug-induced cases included individual necrotic keratinocytes, dense dermal infiltrates, red blood cell extravasation, pigment incontinence, parakeratosis, and substantial eosinophils or neutrophils.[94]

Clinical management

Withdrawal of the culprit

According to the UK guidelines for the management of SJS/TEN, withdrawal of the culprit drug and multidisciplinary supportive care should be prioritized over systemic treatment due to the paucity of evidence regarding the efficacy of such treatments.[79] Withdrawal commonly leads to amelioration of the disorder.

Interdisciplinary team

Due to the high morbidity and mortality of SJS/TEN, multidisciplinary care in a specialized burn unit is recommended for these patients. UK guidelines suggest transferring patients to a burn center if they have TEN and evidence of the following manifestations: clinical deterioration, extension of epidermal detachment, sub-epidermal pus, local sepsis, wound conversion, and/or delayed healing.[79]

SJS/TEN may affect many organs and can have a life-threatening clinical course, requiring risk management.[6,7,79,88,89,95–97] This is best achieved by integrating physicians and other healthcare providers in the clinical management. Apart from dermatologists, the interdisciplinary team should include expert internists specializing in intensive care, hepatologists, gastroenterologists, ophthalmologists, ENT (ear, nose, and throat) specialists, gynecologists, nephrologists, urologists, microbiologists, oncologists, and immunologists.

Supportive care

The supportive management of SJS/TEN patients is similar to the management of severe burn patients, requiring treatment in a burn unit, and has been carefully summarized in detail.[79] More specifically, it includes protecting and restoring the barrier function of the skin, maintaining fluid balance, protecting the airway, and treating infections. Fluid and electrolyte monitoring and replacement are essential. Nutritional support is also needed due to the high catabolic state. Furthermore, thermoregulation and adequate analgesia are usually necessary. There are no clinical guidelines for the skin care of patients with SJS/TEN. Debridement of necrotic epidermis was recommended in the past but is now considered unnecessary. Detached epidermis is regarded as a natural biological dressing that hastens re-epithelialization.[79]

Drug treatment

There is concern that a universally accepted guideline is missing to help provide a standard treatment for patients with SJS/TEN at a high professional level.[79,88,89,95–97] Several reasons contribute to this shortcoming: (1) The rarity of SJS/TEN cases at a single specified center makes it difficult to conduct high-quality randomized controlled trials, which would allow the determination of the benefit/risk ratio of a proposed therapy study protocol. (2) Respective multicenter studies are lacking. (3) The majority of published trials are based on retrospective study protocols rather than a prospective approach, which allows for the collection of complete case data and the input of quality data into assessing tools to generate reliable outcomes, avoiding the sequence of poor data in, poor data out. (4) Some studies have been criticized for retrieving incomplete case data retrospectively from hospital databases, governmental authorities, or insurance companies. (5) Defining endpoints was rarely attempted. (6) Studies mostly ignored the need to determine causality for drugs in SJS/TEN using the ALDEN algorithm of 2010, and for associated DILI using the updated RUCAM algorithm of 2016. (7) The heterogeneity of SJS/TEN cohorts was insufficiently considered, which can be classified into SJS/TEN types 1–5 (Table 7): Type 1: SJS/TEN combined with DILI caused by drugs, assessed by both ALDEN and RUCAM. Type 2: SJS/TEN caused by drugs, assessed by ALDEN but not by RUCAM. Type 3: SJS/TEN caused by drugs, assessed by non-ALDEN and non-RUCAM tools. Type 4: SJS/TEN caused by non-drugs, assessed by various tools.Type 5: SJS/TEN caused by unknown culprits.

Japanese guidelines for SJS/TEN recommend early systemic corticosteroids, either alone or in combination with cyclosporine, as the first-line treatment. However, overall drug treatment recommendations in SJS/TEN remain controversial.[79] Consequently, treatment options are only briefly summarized in this article, and readers should consult a recent review on this topic.[79] This article considers, among others, the use of systemic corticosteroids, intravenous immunoglobulin, the combination of systemic corticosteroids and intravenous immunoglobulin, cyclosporine A, tumor necrosis factor-alpha (TNF-α) inhibitors, combinations of biologic anti-TNF-α with corticosteroids or other treatments, and plasmapheresis.

Empirically, systemic corticosteroids are commonly used to treat patients with SJS/TEN,[8,15,79,96–101] but refinement is needed, considering the different SJS/TEN types (Table 7). Given the complexity of SJS/TEN and patient heterogeneity, a personalized approach to targeted therapies should also be considered in the future to optimize short-term and long-term clinical outcomes. In doing so, we will be able to better equip physicians with both the information and tools needed to treat these often life-threatening reactions.[101]

Prognosis

According to a study from the USA,[44] mortality rates for the SJS group were 5.4%, for the SJS/TEN overlap group 14.4%, and for the TEN group 15.3%. Increasing age, chronic kidney disease, pneumonia, sepsis, and malignant neoplasm were all significantly associated with increased odds of mortality and viewed as risk factors.44 Lethality in the presence of DILI was even higher (36%) and reached 44% to 46% in the presence of jaundice, evaluated using the ALDEN and RUCAM algorithms.[5] A total of 15/76 patients died during hospitalization, with a mortality rate of 16.9% for SJS and 29.4% for TEN. As expected, mortality was influenced by the degree of skin detachment.[37] The necrolysis spectrum and SCORTEN scores correlate well with prognosis, although the predictive ability is still variable.[71]

Contrary to general assumptions, there is no evidence that all drugs can cause SJS/TEN. Instead, various drugs are not involved in SJS/TEN type 3 (Table 3), and only certain drugs lead to a severe clinical course with poor outcomes in SJS/TEN type 1 (Table 2). No robust data exist on lethality rates in patients with SJS/TEN type 4 due to non-drug culprits such as arsenic, bacteria, chemical substances, glyphosate, herbs, insecticides, vaccine biologics, and viruses, to name a few (Table 5).

Mechanistic considerations

Reactions leading to SJS/TEN are immune-mediated, type IV,

and thereby delayed-onset reactions that are $CD8^+$ T-cell-driven.[101] This applies, at least for some drugs causing liver injury in SJS/TEN type 1 (Table 2), where the disease is triggered by the innate immune system activated to the adaptive immune system, as shown for various drugs causing DILI in support of HLA.[24,25,78] Drugs causing SJS/TEN type 1 and 2 (Table 2 and 3) are similar to those involved in DILI, which can be classified as either substrates of and metabolized by cytochrome P450 isoforms or not.[102] Interestingly, Amoxicillin-clavulanate is listed as a culprit drug for SJS/TEN type 2 (Table 3) but not type 1 (Table 2), yet it is one of the drugs causing DILI via a mechanism not involving microsomal cytochrome P450.[102] As it stands, uncertainty remains about how hepatic drug metabolism may be involved in the development of the various SJS/TEN types.

At the skin level, immune reactions are caused by small molecule drugs and biologics.[101] The proposed downstream effect of molecules implicated in SJS/TEN is the induction of keratinocyte death. Apoptotic cell death has been proposed as playing a role in the pathogenesis of SJS/TEN, with both the extrinsic and intrinsic pathways leading to caspase-3 activation and keratinocyte death. The extrinsic pathway involves TNF-α, Fas/FasL, and TNF-related apoptosis-inducing ligands, which bind to cell surface death receptors and activate caspase-8, leading to caspase-3-associated cell death.[101] In the intrinsic pathway, $CD8^+$ T-cell-induced cellular stress leads to the release of BAX/BAK, stimulating mitochondrial release of cytochrome c, causing the cleavage of inactive procaspase-9 and activation of caspase-3. Caspase-3 can also be activated by granulysin, perforin, granzyme B, and Fas-ligand released by $CD8^+$ T cells, natural killer cells, and macrophages.[101] Additional aspects of the pathogenesis are provided in various reports recommended for reading.[8,9,22,103–107]

Although much research has been done to clarify pathogenetic issues, it remains unclear why and how some drugs exert dual target properties in SJS/TEN by affecting not only the skin but also the liver (Table 2). Even more exciting is the question of why most drugs affect only the skin without injuring the liver (Table 3), the organ commonly involved in drug metabolism via microsomal cytochrome P450[102] with potential assistance from HLA.[78] There is still a long way to go before pathogenetic features are detected for individual culprits of SJS/TEN.

Conclusions

The previous inhomogeneity of SJS/TEN cohorts made it almost impossible to clearly define its clinical features, personalized treatment options, and pathogenetic steps leading to this complex disorder. However, the newly presented SJS/TEN typology will help collect homogeneous study cohorts and contribute to a better understanding of the specifics of SJS/TEN. Current views suggest immune mechanisms as crucial in the development of SJS/TEN caused by some drugs, through activation of the innate immune system to the adaptive immune system. Presently, it seems premature to clearly define the mechanistic steps for each drug and non-drug culprit of SJS/TEN. Future studies should be prospective and assess all suspected drugs for causality using the updated RUCAM for DILI and the ALDEN algorithm for SJS/TEN. Much work remains ahead to provide evidence-based data that will allow for the recommendation of personalized therapies supported by well-conducted randomized controlled trials.

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Conflict of interest

RT has been an Associate Editor of Journal of Clinical and Translational Hepatology since 2013.

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