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Review

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis- An Overview

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Abstract: Both Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are main injurious cutaneous medication reactions that mostly affect the epidermis and mucus membranes. TEN and SJS affecting nearly 1 or 2/1,000,000 people per year, and can recognized as medical crises since they may be deadly. Mucocutaneous discomfort, hemorrhagic erosions, erythema, and more or less severe epidermal separation that appear as ulcer and patches of dermic loss are their defining characteristics. The sole difference between TEN and SJS at this time is the degree of skin detachment, making them two extremes of a spectrum of severe cutaneous adverse drug reactions (cADRs). In the majority of cases, drugs are considered as the principal reason of SJS/TEN, but herpes simplex virus and Mycoplasma pneumoniae infections are also recognized causes, along with lesser number of cases in which the cause is still unknown. Among the drugs with a "high" likelihood of producing TEN/SJS are carbamazepine (CBZ), trimethoprim-sulfamethoxazole, phenytoin, aminopenicillins, allopurinol, cephalosporins, other sulfonamide antibiotics, quinolones, phenobarbital, and NSAIDs of the oxicam variety. There is strong genetic evidence for SJS and TEN in Han Chinese due to the substantial association between the human leukocyte antigen (HLA-B*1502) and SJS brought on by CBZ. The diagnosis is made mostly based on clinical symptoms and the histological study of a dermal biopsy. Pemphigus vulgaris, bullous pemphigoid, linear IgA dermatosis, paraneoplastic pemphigus, disseminated fixed bullous drug eruption, acute generalized exanthematous pustulosis (AGEP), and staphylococcal scalded skin syndrome (SSSS) are among the differential diagnoses. The management of patients with SJS/TEN is complicated by the high risk of mortality, necessitating early diagnosis, estimation of the SCORTEN prognosis, identification and discontinuation of the causative drug, specialized supportive care, and high-dose injectable Ig therapeutic interventions. The reported fatality rates for SJS are 1-5% on average and 25-35% for TEN; it can be even higher in patients who are elderly or who have a significant amount of epidermal detachment on their skin. More than 50% of TEN patients who survive the disease experience long-term consequences.

Keywords: SJS; TEN; Adverse drug reactions

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1. Introduction

In 1922, two young boys with acute mucocutaneous disease were the first to be diagnosed with Stevens-Johnson syndrome (SJS) [1]. Severe purulent conjunctivitis, severe stomatitis, purpuric macules, and severe mucosal necrosis were the main symptoms of the disorder. It was identified as SJS and characterized as an acute mucocutaneous disorder that is typically drug induced, has a protracted course, and has the potential to be lethal. A distinction should be made between it and erythema multiforme (EM) majus. Latest clinical research has demonstrated that SJS should not be referred to as an "EM majus," as these illnesses are unique from one another [2].

The condition known as toxic epidermal necrolysis (TEN), was first identified in four patients in 1956 by Alan Lyell [3]. The findings that TEN was drug-induced and that specific medicines, including pyrazolones, sulfonamides, antiepileptics, and barbiturates were the most frequently reported initiations of TEN didn't occur until additional patients with the condition were found in many years after Lyell's publication. The extent of skin detachment is now the only distinction between SJS and TEN, making them the two extremes of a spectrum of severe epidermolytic cADRs [3].

2. Epidemiology of SJS and TEN

SJS & TEN are uncommon conditions in terms of total prevalence; in 1996, there were 1.89/1000000 instances of TEN per year in Berlin and Western part of Germany [4]. Similar findings are published by La Grenade et al, who estimate that every year there are 1.9 cases of TEN per million people in the USA (according to the FDA AERS database) [5]. Chan et al. observed lower incidence rates in Singapore [6]. SJS, the less severe variant, is three times more prevalent than TEN, with reports of 2-7/1000000 individuals each year. Patients who have HIV in addition to cancer, particularly cancers related to haematology, are also more likely to develop SJS/TEN. Mortality rates for TEN and SJS combined are 50% and 10%, respectively with a combined rate of 30%. Both are more common in women than men, and they affect people of all ages. Greater mortality is linked to older age (more than 70) and comorbidities.

The prevalence of SJS and TEN can vary significantly depending on the region, patient genetics (HLA, metabolising enzymes), the presence of concurrent malignancy, or concurrent radiation [11,12]. According to genome-wide association studies (GWAS), the HLA-B 15:02 allele increases risk in Han Chinese population who are taking carbamazepine (CBZ) as their treatment therapy. Studies have also revealed a connection between the HLA-B 58:01 allele and allopurinol-induced TEN/SJS in populations from Europe and Asia.

3. Clinical Signs and Symptoms

3.1. Acute Phase

Initial sings of SJS and TEN may be vague and symptoms including fever, discomfort in swallowing, and stinging eyes. These symptoms typically appear a few days before cutaneous signs. The presternal section of

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the trunk and the face, early locations of cutaneous involvement include the soles of the hands and the palms. More than 90% of individuals develop buccal, vaginal, and/or ocular mucosa participation (erythema and erosions), and occasionally affect the respiratory and gastrointestinal tracts [7,8]. Optic participation at disease onset is common and may include acute conjunctivitis, ocular discharge, swelling of eyelid and erythema [9]. However, the harshness of early complications is not always indicative of later difficulties. Initial skin lesions contain erythematous and livid macules as part of their morphology. They may or may not be somewhat infiltrated, and they often coalesce quickly [8]. The mentioned mucosal involvement and skin symptoms require for the prompt cryosection of a skin sample in order to begin a speedy diagnostic confirmation. Histopathological analysis, which includes direct light microscopy analysis of skin biopsy, is essential to rule out diagnostic information like bullous fixed drug eruption, autoimmune blistering diseases, acute generalized exanthematic pustulosis, and because of its rareness in adults, to a lesser extent SSS syndrome [10].

Excessive areas of epidermal separation form during the second phase. Applying tangential mechanical pressure to a number of erythematous zones should be used to conduct a more thorough skin inspection in the absence of epidermal separation (Nikolsky sign). The Nikolsky sign is present when mechanical pressure results in epidermis detachment, although it is not exclusive to TEN or SJS as it can also be present in other skin conditions such autoimmune bullous disorders [11].

An important prognostic factor is the measure of the amount of dermic participation. It should be underlined that the estimation of the level of dermic participation should only include necrotic skin that has detached already.

3.2. Late phase and its sequelae

Sequelae are frequently observed in late stages TEN. The following symptoms are present, in study by Magina et al. [12], eye problems (37.5%), nail dystrophies (37.5%), and hyper and hypopigmentation of the dermic (62.5%) . Yip et al.[13] found that 50% of TEN patients experience late ocular sequelae, including corneal ulcers (2%), lagophthalmos (2%), trichiasis (16%), distichiasis (14%), symblepharon (14%), entropion (5%), vision loss (5%), and ankyloblepharon (2%), in decreasing order of frequency [13]. Only a very small percentage of patients have hypertrophic scars [14]. Long-term issues affect 73% of patients who report having acute involvement of mucosa, and the oral and esophageal mucosa are most commonly affected, with lung and vaginal mucosa being less affected [15]. In a relatively short post-SJS/TEN investigation, 7 out of 9 patients showed symptoms resembling keratoconjunctivitis, xerostomia, or both [16,17].

4. Etiology and Pathogenesis of SJS/TEN

4.1. Genetic susceptibility

Investigations into the complex subject of genetic factors connected to drug hypersensitivity have been conducted in a variety of cultures and ethnic backgrounds. The HLA-B 1502, SJS, and carbamazepine were

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found to be significantly correlated in Han Chinese patients in previous studies, revealing a novel and significant link among HLA, drug hypersensitivity, and ethnicity [20–22].

As a result of this strong association, which had an odds ratio of 2504, more investigations in the patients having a similar ethnicity of Hong Kong Han Chinese with severe ADRs to antiepileptic medicines were done [20]. The vulnerability of persons with HLA-B*1502 to CBZ in population of Thai was validated by a different investigation [23]. However, a smaller study conducted in India found little evidence of a link among HLA-B 1502 and severe medication allergies brought on by carbamazepine. However, no genetic correlation could be demonstrated in Europeans or Japanese [24,25]. In a significant European investigation, patients' HLA-B genotyping was done (RegiSCAR) who had experienced severe cutaneous side effects from the two drugs already mentioned (CBZ and allopurinol) as well as from three additional risky medications (sulfamethoxazole, lamotrigine, and NSAIDs of the oxicam type). This RegiSCAR analysis found that HLA-B*1502 is neither a biomarker for oxicam-type drugs that cause SJS/TEN, such as carbamazepine, sulfamethoxazole, lamotrigine, nor an adequate explanation for the disease's origin in Europeans [24,26]. This is concluded that HLA-B*1502 is not independent of population indicator for SJS/TEN in those who have taken CBZ. In HLA-B*1502 participants, severe cutaneous responses were not only linked to CBZ but, to a smaller extent (lower OR), to lamotrigine and phenytoin as well [27,28].

A second significant association between SJS/TEN and HLA genotype has been reported for allopurinol. In fact, HLA-B*5801 was shown to be present in all Han Chinese patients who had a severe ADR to allopurinol [29]. Then, a significant association of HLA-B*5801 and SJS/ TEN was discovered in individuals from Japan [30], Thailand [31], and to a lesser level (in 55% of cases), individuals from Europe [26].

5. Pathological mechanism of SJS/TEN

Even though the pathophysiology of SJS/TEN is not entirely understood, it is supposed to be immune-mediated because the condition can return fast when a person is given the same medication again [32]. The pathogenic cause of the widespread epidermal detachment observed in SJS/TEN is keratinocyte apoptosis followed by necrosis, according to the histology of the lesions. The clinical, immunological, and histological findings in SJS/TEN are consistent with the generally recognised view that SJS and TEN are distinct drug hypersensitivity reactions, with cytotoxic T lymphocytes (CTL) contributing to the early phase. In fact, throughout the early stages of the disease, cytotoxic CD8+T cells predominate in blister fluid. [33], showing that a drug presentation that is MHC class I restricted results in clonal growth of CD8+ CTLs and the consequent, as of this writing, poorly understood immunological reaction that results in SJS/TEN. These CD8+ T lymphocytes lack CD45RA and CD28 and express the cutaneous leukocyte antigen (CLA). Blister T cells from patients have been shown to have Nassif et al study on a drug's specific cytototoxic impact on keratinocytes and autologous B-lymphocyte cell lines [34,35], and also proved that granzyme B was the mediator of this

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cell-mediated cytotoxicity. The paucity of immune cell infiltration, including CTLs, in the patient's skin with SJS/TEN and the enormous keratinocyte apoptosis have led to the current seek for cytotoxic proteins and/or cytokines that might also "amplify" the severity of keratinocyte apoptosis that CTLs alone can stimulate upon cell-cell contact. The greatest evidence to date suggests that the cytotoxic molecules FasL [36] and granulysin [37] play a key part in the widespread keratinocyte apoptosis in SJS/TEN.

Research employing a TEN lesioned skin biopsy cryostat slice in an ex vivo experimental setting overlaid with The function of the membrane form of the death ligand FasL and its associated death receptor is supported by Fas-expressing lymphoid target cells. Fas in keratinocyte apoptosis-initiating signaling [36]. There are concerns about the functional significance of rise keratinocyte membrane FasL and its ability to trigger keratinocyte cell death because the ex-vivo case of the lytic potential of keratinocyte FasL in TEN was confined in its effect on lymphoid target cells and did not demonstrate with keratinocytes as target cells. It is well recognized that interferon gamma, a cytokine believed to be found in the skin during TEN, and primary keratinocytes are both vulnerable to the cytolytic effect of FasL in vitro, might make this sensitivity even more acute [34,38].

Nevertheless, it remains unknown what causes the immune system, especially T cells observed in blister fluid at the beginning of the condition, to regulate the up-regulation of FasL/Fas on keratinocytes. It is still debatable how soluble FasL (sFasL) affects SJS/TEN. It is now apparent that patients with SJS/TEN have blood levels of sFasL that are raised up, and that these levels are consistently raised when testing is done before skin detachment [39]. However, because soluble FasL is far less effective at destroying cells than membrane-bound FasL, it is doubtful to be the source of keratinocyte apoptosis in TEN [34,38]. However, one study found that SJS/TEN patients' peripheral blood monocytes induced by the causative drug excreted high levels of sFasL, and that these patients' sera were able to induce a lot of keratinocyte apoptosis [40], However, it must be distinguished that sera can also contain small membrane vesicles with membrane-bound FasL, which could explain the observed activity [40].

Through gene expression analysis of blister fluid cells and examination of blister fluid from SJS/TEN patients, secretion granulysin, a covalent cytostatic protein secreted by CTLs, NK cells, and NKT cells, has most recently been discovered to be an important molecule responsible for the formation of keratinocyte death in TEN [37]. Granulysin mRNA is highly expressed in blister fluid cells, the protein is present in higher proportions in ulcer fluid, and also utmost critically, intradermal injection of recombinant granulysin in mice mimics the symptoms of SJS/TEN. Granulysin may have a significant role in SJS/TEN, as further evidenced by the discovery that high serum granulysin values appear to distinguish between serious and non-blistering adverse medication reactions, with serum granulysin levels generally normal in the latter [37].

As a result, and based on what we now know, CD8 T-cells are important participants in the pathogenesis of SJS/TEN, and also the cytolytic molecules FasL and granulysin. Current study focuses on how a suspect

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medicine governs the activity of these crucial actors in a specific patient, might grow SJS/TEN.

6. Drugs

The majority of cases of SJS/TEN are triggered by drug exposure and an associated hypersensitivity reaction. Allopurinol is the leading frequent reason of SJS/TEN in Europe and Israel in terms of absolute number of cases [29,30], and this is particularly true for individuals taking daily dosages of minimum 200 mg.

In a case-control study of patients who were hospitalised for SJS/TEN between 1989 and 1993 in France hospitals, Germany, Italy, and Portugal, Trimetroprim-Sulfamethoxazole and other sulfonamide antibiotics drugs are more likely to cause SJS/TEN when used for a short period. The danger of initiation of SJS/TEN is highest during the first two months of treatment for medications that are typically taken for prolonged periods of time (CBZ, PHT, PBT, VPA, NSAIDs of the oxicam-type, corticosteroids, and allopurinol), with a subsequent sharp decline in incidence [2,32,41,42]. Although the relative danger of these medicines is higher than that of other medications, the actual danger is still modest, with 5 cases or fewer per million users per week. Mockenhaupt et al. analysed a comparable population during 1997 and 2001 in large-scale case-control research in Europe that included more than 100 million people and paid particular attention to recently marketed medications [43]. However, when getting treatment with VPA, the adjunctive therapy of other drugs, such as lamotrigine, can obscure the frequency of SJS/TEN [44]. CBZ (1.4 cases per 10,000 users), LTG (2.5), PBT (8.1), and PHT (8.3) all carried a considerably increased risk of developing SJS/TEN. Nearly all instances of SJS/TEN developed within 63 days of initiating to take antiepileptic medications, according to Mockenhaupt et al. Valproic acid had a modest incidence compared to certain other antiepileptic drugs, with 0.4 occurrences per 10,000 users [45]. Additionally, research on various communities demonstrate that the chance of developing SJS/TEN is maximum just after starting medication and declines after 8 weeks or longer of treatment [46]. It is noteworthy to note that long-term usage of glucocorticosteroids for a range of illnesses has no effect on the frequency of SJS/TEN incidence for the pharmaceuticals in question, but it seems that glucocorticoids increases the period between the commencement of drug consumption and the onset of SJS/TEN [47]. According to recent study on pediatric TEN, children may be more sensitive to acetaminophen than adults are and similar medications to those used in adults are being employed [48]. Rare cases of photo-induced TEN or SJS have been documented. There are case studies available for clobazam, naproxene, and hydroxychloroquine [49–51].

One issue that comes up regularly is the initiation of TEN or SJS after immunisation. Despite the likelihood of a connection among vaccination and SJS/TEN, the vaccine reporting of adverse events system concludes that the benefits of immunizations outweigh the potential risk of SJS/TEN due to the very small number of cases compared to the high number of vaccines [52].

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7. Diagnosis and diagnostic methods

The analysis is dependent on both histology characteristics and clinical symptoms. Initial erythematous and livid macules on the dermic, with a positive Nikolsky sign can be caused by mechanical pressure on the skin, are typical clinical indications. Within seconds to hours, epidermal detachment, which is defined by the development of ulcers, then follows. However, it had better be highlighted that the Nikolsky sign does not only apply to SJS/TEN. In nearly all cases, mucosal involvement—including optic involvement—progresses before or at the same time as cutaneous symptoms. The key differentiating feature between SJS, overlapping of SJS and TEN, and TEN is the surface area of the skin which is separated [53,54].

8. Differential diagnosis

Acute generalised exanthematous pustulosis (AGEP), widespread fixed bullous drug eruption, bullous pemphigoid, linear IgA dermatosis, paraneoplastic pemphigus, staphylococcal scalded skin syndrome (SSSS), and pemphigus vulgaris are among the major differential diagnoses of SJS/TEN. SSSS was once among the furthermost significant variance analyses, but today there are only between 0.09 and 0.13 cases per million people year, a very low incidence [55].

9. Management and Therapy

9.1. Treatment in acute stage

The following steps must be taken in order to manage the acute stage of the disease: sequentially assessing the severity and prognosis of the illness; promptly identifying and withdrawing the offending drug(s); swiftly launching helpful care in the proper set; and ultimately, "specific" medication treatment, as explained in more detail below.

9.2. Rapid assessment of severity and prognosis

The seriousness and the disease's prognosis should be established as soon as SJS or TEN has been diagnosed in order to specify the ideal medical environment for ongoing therapy. The established SCORTEN disorder severity rating scheme can be used to assess diagnosis in SJS/TEN patients. If at all possible, SCORTEN patients score of 3 or higher should be be able to in a severe care unit[56,57].

9.3. Prompt withdrawal of causative drug(s)

When lesions or erosions develop during a drug eruption, prompt drug withdrawal should be a top priority. Garcia-Doval et al. have demonstrated that patients subjected to causal medications with lengthy half-lives have a higher probability of dying [58], and that the faster the responsible treatment is discontinued, the better the diagnosis. It is crucial to consider the drug's administration history and its alleged capacity to produce SJS/TEN in order to pinpoint the offending drug(s). The majority of the time, the interval between the first dose of a culprit medicine and the onset of SJS/TEN is between 1 and 4 weeks. You can find infor-

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mation about the reported potential or possibility that a medicine will result in SJS/TEN in Pubmed/Medline or other pertinent sources like the Litt's medication eruption reference guide [59].

9.4. Supportive Care

Because SJS/TEN poses a hazard to human lifespan, supportive therapy is a crucial component of the therapeutic strategy [60,61] According to a study done in the USA that involved 15 regional burn centres in which 199 patients were admitted, regardless of the severity of their condition, patients who were admitted to burn unit within 1 week of the commencement of their disease had a substantially larger survivability than those who were admitted after that point (29.8% vs. 51.4%, $p<0.05$) (APACHE-score and TBSA = Total body surface area) [62].

Age, followed by the degree of sepsis at the moment of admission and, to a minor extent, the percentage of the total surface of the body involved, was found to be the most significant negative prognostic factor in a previous study conducted on the outcomes of patients after admitted to a burn center. When other factors are present, co-morbidities and steroid use lose some of their significance, even if they may still be important on an individualized level [62,63]. The management of electrolyte and fluid requirements is a crucial component of supportive care. To sustain urine production of 50–80 mL per hour, intravenously fluid should be administered. This fluid should contain 0.5% NaCl and 20 mEq of KCl. In cases of frequently occurring hyponatremia, hypokalemia, or hypophosphatemia, appropriate rapid and aggressive replacement therapy is needed [61,64]. Wounds should be successfully treated without skin exfoliation since inflamed skin acts as a basic biological barrier that likely encourages re-epithelialization, Skin exfoliation is frequently performed in burn units. Non-adhesive medicaments are used as necessary, and external sulfa-containing medications should be ignored[65].

9.5. Drug Therapy

Unfortunately, there is not yet a single treatment for SJS/TEN has demonstrated effectiveness in rigorous medical trials. In regard to supportive therapy, a number of therapy approaches have been documented in the literature; they are mentioned below and shown in Figure 1. Systemic steroids were the go-to therapy up until the early 1990s, but controlled studies have not demonstrated any benefits. Their use has come under increasing scrutiny due to a lack of compelling proof of their usefulness as well as the confusion brought on by the variety of steroid treatment regimens that have been reported (short-term versus long-term, variable dose regimens). A term "pulse" of high dosage corticosteroids (dexamethasone), according to a recent retrospective monocenter trial, may be beneficial [66]. On the contrary hand, corticosteroids did not appear to have a substantial impact on the mortality when compared with supportive care alone, according to a recent surveying case-control study performed by Schneck et. al. in France and Germany [67].

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9.5.1. Thalidomide

Thalidomide, a recognised immunomodulator and anti-angiogenetic drug with anti-TNFa action, has been investigated in the therapy of TEN. However, a double-blind, controlled, placebo-controlled study found that the thalidomide-treated group had a higher death rate than the control group, showing that thalidomide is dangerous for TEN [68].

9.5.2. High-dose intravenous immunoglobulins.

After it was discovered that pooled person intravenous immunoglobulins (IVIG) have anti-Fas capability in vitro, IVIG were examined for the therapy of TEN, and their effects were documented in a variety of uncontrolled investigations [69]. The antimicrobial efficacy of IVIG in TEN has been examined in several published studies and 12 uncontrolled clinical studies with 10 patients or more to date. With the exception of few researches, all studies support IVIG's great tolerability and minimal hazardous potential when used with the necessary caution in individuals who may be at risk for adverse events. Together, despite the fact that each trial has its own possible biases and that the 12 investigation are not exactly applicable, 9 studies out of the 12 studies raise the possibility that high-dosage IVIG might reduce the mortality linked to TEN [70]. According to a review of published research, total IVIG dosages greater than or equal to 2 g/kg may be more beneficial than dosages of 2 g/Kg maybe low. Trent et al. reviewed the literature between a period of 1992 to 2006 and selected all individual research in which the dosages of IVIG prescribed for each patient was noted, ignored cases that emerged in copy in various papers, and used a logistic regression multivariate analysis to assess fatalities and overall IVIG dosages within a week of adjusting for age and the injured body surface. Each 1 g/Kg rise in the IVIG treatment was connected to a statistically significant 4.2-fold improvement in TEN survival rates. Regression analysis results were obtained despite the study's limitations, which the authors themselves recognise and which include systematic bias, the diverse diagnostic definitions and techniques of each research, as well as the isolation of two experiments because they lacked information on the precise IVIG dosages. Particularly, the mortality was 0% in the subgroup of 30 treated group with a total dosage of further above 3 g/kg of IVIG, demonstrating that patients administered with high doses of IVIG show lower mortality compared to those administered with low dosages. The authors believe that early presidency of elevated Ig (3 g/kg total dosages given over 3–4 days) must be taken into consideration in addition to helpful support for the treatment of TEN due to the lack of other validated specific alternative treatment and the preferable side-effect profile of IVIG. It is still debatable whether corticosteroids or immunosuppressive medications should be used concurrently. A few kids with SJS/TEN have also received IVIG, and two uncontrolled studies point to a potential benefit[71].

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9.5.3. Ciclosporin

Ciclosporin (CsA). A successful treatment for autoimmune disorders and transplantation is CsA, a calcineurin inhibitor. Arevalo et al. conducted a case-series analysis with two treatment options: CsA alone versus cyclophosphamide plus corticosteroids. Patients receiving CsA took noticeably less time to complete re-epithelialization, and fewer patients experienced multi-organ failure and died [72]. The course of the disease was stopped within 72 hours in a small case series involving three TEN patients who were first given high doses of intravenous dexamethasone and then given CsA [73]. The use of CsA in TEN was also observed to have a beneficial effect in other single case reports [74,75]. A recent open, phase II trial was done by Valeyrie-Allanore L to evaluate the safety and potential benefits of ciclosporin [76]. In the trial, 29 patients were included (10 with SJS, 12 with SJS-TEN overlap, and 7 with TEN). Of these, 26 patients successfully completed the oral CsA treatment (3 mg/kg/d for 10 days, then reduced over a month). The prognosis score indicated 2.75 fatalities, although none actually happened ($p = 0.1$), indicating that ciclosporin may be helpful for treating TEN even though it is not statistically significant [76].

9.5.4. TNF inhibitors

Hunger et al. have suggested a novel therapeutic strategy for treating the proinflammatory cytokine TNFa. They administered the chimeric anti-TNFa antibody (infliximab 5 mg/kg) to one patient in a single dosage, and they observed that the patient's illness development stopped within 1 day, proceeded by a complete re-epithelialization within 5 days [77]. Researchers also discuss 3 cases of acute widespread exanthematous pustulosis, TEN, and infliximab treatment response [78]. In one example, treatment with the soluble TNFa Receptor Etanercept 25 mg on days 4 and 8 after the onset of TEN caused the epidermal detachment to stop within 24 hours, however the patient afterwards passed away. So far, there is not enough published data to make any judgments about the potential role of TNF antagonists in TEN.

9.5.5. Plasma exchange/plasmapheresis (PE).

PE has also been tested in SJS/TEN, but the information currently available prevents drawing any conclusions about the efficacy of this strategy due to the small sample size, the normal confounding factors, such as distinct or combined medications, and other potential biases [79,80]. Furthermore, no differences in mortality were seen in a small, single retrospective investigation employing PE, which compares the clinical study to two published case series treated as controls [81].

9.5.6. Cyclophosphamide (CPP).

Small case series have examined CPP, either alone [82] or in conjunction with other actions such CsA [72,83], as well as high-dose corticosteroids [84]. Larger research studies are required to explain these initial results with a specific emphasis to possible adverse effects, despite the fact that the authors of these modest experiments suggest that CPP has a positive effect.

10. Treatment of sequelae

Due to the frequent simultaneous involvement of the skin, eyes, and mucous membranes, the monitoring and treatment of sequelae should be interdisciplinary (oral, gastrointestinal, pulmonary, vaginal, as well as urine). The prevention of ocular problems needs special consideration. It is essential to consult an ophthalmologist as soon as possible to determine the severity of the ocular involvement and to begin therapy with topical steroids. Patients who undergo particular ophtalmological treatment during the first week of disease are said to have much superior visual outcomes[85]. Ophthalmic steroids and/or intensive eye lubrication may occasionally be needed to treat ocular problems with

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an inflammatory origin and stop them from progressing to the point where a corneal transplant is ultimately necessary [86]. In a brief, single retrospective investigation, IVIG had no discernible effects on the frequency or severity of ocular problems, but the study's power was poor [70].

It is unclear what advantage local antibiotic therapy (ointments) provide. According to Yip et al., local antibiotic therapy causes more long-term problems, such as, for instance, dry eyes [87]. Long-term problems such as dysphagia, oesophageal strictures, and hypopharyngeal stenosis are challenging to cure [88] and may necessitate laryngectomy.

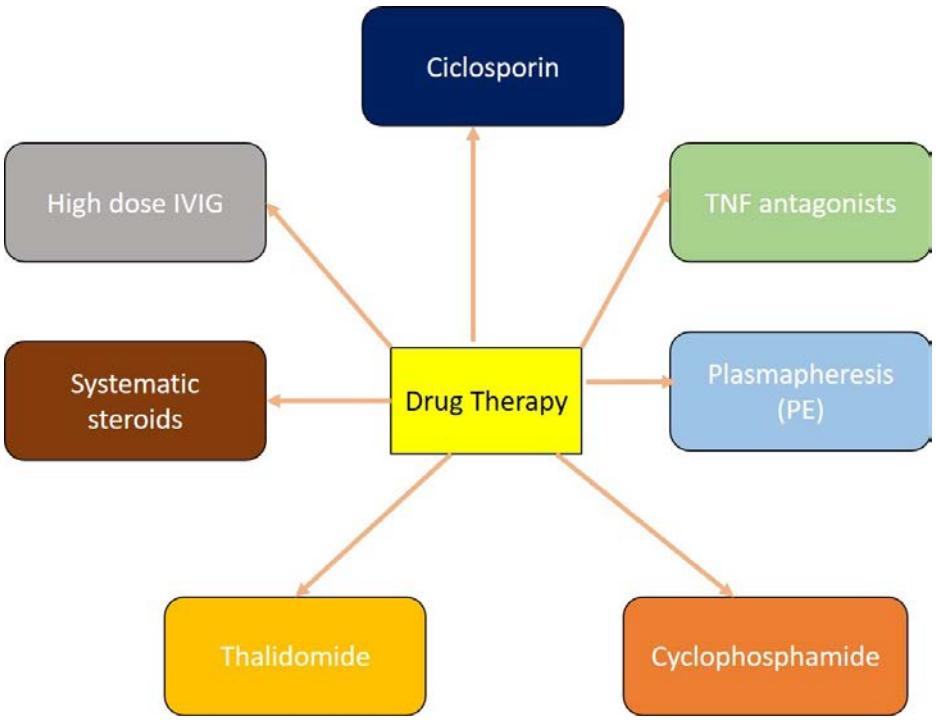

Figure 1. Various drug therapies for the treatment of SJS/TEN.

11. Allergological testing

When attempting to pinpoint the substance responsible for SJS/TEN, a thorough drug history is crucial. When there are several possible drugs, allergological screening can be helpful in selecting the much more likely target. The intensity of SJS and TEN forbids re-challenge and subcutaneous screening with the offending medications because of the perceived danger of doing so, despite the fact that two case reports have recorded intradermal testing without causing a second episode of TEN [89]. However, after local ocular therapy, induction of SJS/TEN has been described [90]. Patch-testing is an experimental approach; however, it is not currently a common diagnostic method. Only two of 22 evaluated patients got a positive significant patch test, demonstrating that limited susceptibility is a concern with patch screening in SJS/TEN in a previous study [91]. Currently, ex vivo/in vitro assays are mainly the focus of allergological testing. Patients who are allergic to beta-lactam antibiotics can be detected with a sensitivity of 60–70% using the lymphocyte transformation test (LTT), which assesses the propagation of T cells to a medication in vitro [92]. Unfortunately, even when done within a week after the disease's beginning, the LTT's sensitivity is still relatively low in SJS/TEN [93]. Another method that has recently been described looks for an increase in CD69 expression on T-lymphocytes 2 days after lymphocyte stimulation in vitro as an indicator of drug sensitization [94]. There is still a need for innovative in vitro techniques to identify the substance that caused SJS/TEN.

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12. Prognosis

SJS and TEN are serious and potentially fatal diseases. The usual recorded mortality rate for SJS is 1-5%, whereas the average reported death rate for TEN is 25–35%; it may even be greater in older patients and those who have an extensive epidermal separation [95–97]. Different criteria systems have been proposed to regulate the danger assessment and diagnosis in affected role with SJS/TEN. The SCORTEN, which examines the following factors, is currently the most popular scoring system. These factors are age, malignancy, tachycardia, early body surface area of bicarbonate, epidermal disinterestedness, serum urea, and serum glucose. Lactate dehydrogenase (LDH) may serve as an extra helpful criterion in the assessment of illness severity, according to a recent publication by Yun et al [98].

Over 50% of TEN patients who survive the disease experience long-term consequences. These include nail dystrophy, generalized hair loss, phimosis, vaginal synechiae, conjunctival synechiae, entropion, ingrowth of eyelashes, cutaneous scarring, uneven pigment, eruptive nevi, and recurrent attritions of the mucous lining.

13. Conclusion

Recent developments in the immunogenomics and immunopathogenesis of SJS/TEN have been significant. Nevertheless, there are still a number of clinical and research gaps. We require biomarkers for early diagnosis and prognosis. They can be found in exhaled air as well as serum, providing a non-invasive way to measure inflammation. There are no recommendations for therapeutic therapy or genetic predictors for the majority of medicines that cause SJS/TEN that are based on good quality studies or meta-analyses. Furthermore, it is currently unknown why just a small portion of the population (10%) with an HLA risk allele may experience SJS/TEN after being exposed to the causative drugs. More research is required to fully understand the aetiology of SJS/TEN in order to ensure an early diagnosis and a successful course of treatment.

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