Pathophysiology and management of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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Abstract

Background: Epidermal necrolysis (EN) is an acute mucocutaneous reaction syndrome characterized by extensive necrosis and epidermal exfoliation and can cause death. The initial lesion is in the form of erythematous macules, then progressively grow to sagging blister lesion and subsequent epidermal peeling. The causes of SJS and TEN may vary such as infections, vaccinations, drugs, systemic diseases, and food. However, the main cause is the drug as found in many cases.

Methods: The pathophysiology of the EN is still unclear. Pathologically, tissue damage in the form of epidermal necrolysis is a picture of mass keratinocyte cell death through apoptosis. The stimuli that can induce apoptosis include cellular stress, DNA damage and intracellular cytokines. It may as a result of the role of cytotoxic T cells against keratinocytes, through perforin-granzyme B or Fas-FasL interactions and granulysin. Another theory of SJS-TEN pathophysiology is the slow acetylation (drug metabolic disorder) and the theory of genetic susceptibility.

Result: Finally, we include a comprehensive review of well-established widely available therapies in SJS-TEN patients.

Discussion: It requires rapid diagnosis, suspension of suspected drug as soon as possible, supportive therapy and specific therapy

Conclusion: An understanding of the pathophysiology and current management of SJS and TEN is expected to assist in the prevention of disease and early diagnosis and can provide more effective therapy for SJS-TEN treatment

Keywords: Epidermal necrolysis, SJS-TEN, perforin-granzyme B, Fas-FasL interactions, granulysin

Background

Epidermal necrolysis (EN) is an acute mucocutaneous reaction syndrome characterized by extensive necrosis and epidermal exfoliation and can cause death. The initial lesion is in the form of erythematous macules, then progressively grow to sagging blister lesion and subsequent epidermal peeling.1 Based on the body surface area involved, EN is classified as follows into three; they are Stevens-Johnson Syndrome (SJS) if lesion area <10%, overlap of SJS toxic epidermal necrolysis (SJS-TEN) if the lesion area is 1030% and TEN if the lesion area is> 30%.5,6

The incidence of EN in Europe and the United States is estimated to be one up to six cases per one million patients per year, and occurs less frequently in men with a sex ratio of 0.6.1 The incidence rate of this case remains unknown in Indonesia. Based on a retrospective study in Palembang, a high SJS incidence rate was found in dr. Moewardi Hospital period 2006-2008 affecting 43 people, whereas 10 causes was found in dr. Moewardi in January 2015 - May 2016.3,4 SJS-EN cases are most often found after the fourth decade.1 However, this condition also occurs in children aged 3 months. Stevens Johnson-EN syndrome is more common in the Caucasian race.5 The incidence rate in children is lower than in adults and has a better prognosis.6 Increased age, comorbidity and wider skin involvement are correlated with poor prognosis.1

Epidermal necrolysis are life-threatening diseases that require quick and prompt treatment, recognize and stop immediately the causative
drugs (in dubious cases, stopping all drugs consumed within 8 weeks before onset) and treat patients in the hospital. In addition, the pathophysiology of the EN is still unclear. Based on this statement, the literature review is intended to better understand the pathophysiology and current management of EN.

Etiology

The causes of SJS and TEN may vary they include infections, vaccinations, drugs, systemic diseases, and food. However, the main cause is the drugs as found in many cases. In SJS, 50% of cases are associated with drug exposure and more than 100 different drugs have been reported as the causes. Mycoplasma pneumoniae can cause SJS in children. EN diagnosis is mainly based on clinical symptoms of a macular morbilliform rash accompanied by an uneven form of purpura and the lesions are usually not itchy. The eruption is usually symmetrical on the face, upper part of the body and when there is a diffuse with a blister and signed by a positive Nikolsky, but this mark is not typical for SJS or TEN. The bull usually occurs in the eyes, ears, noses, and the fragile genital area and it is leaving the area of redness so that it will look like a wet dermis (oozing). A necrotizing epidermis will be seen as a peel skin similar to a second-degree burn. The occurrence of EN disease usually occurs after the consumption of the drug with a duration of 4-30 days, preceded by prodromal symptoms 1-14 days, such as fever or flu symptoms, headache, malaise, sore throat, myalgia and rhinitis, sometimes vomiting and diarrhea. The initial SJS eruption usually involves erythema macule with an atypical target lesion resembling erythema multiforme, resulting in frequent misdiagnosis. However, these atypical target lesions are not always obtained.

The causes of SJS and TEN may vary. Four categories of etiology include infection, drugs, associated with malignancy and idiopathic, but the main cause are drugs. More than 100 different drugs have been reported as likely causes. Treatment of a single drug can predict the drug as the cause in 60-79% of cases and the reaction usually occurs between 4 to 30 days after the initial exposure. Drugs that are used for long-term such as carbamazepine, phenytoin, phenobarbital, allopurinol, the highest culprit of SJS within the first 2 months drug consumption. Other causes are immunization, chemical substances, bone marrow transplant and radiotherapy.

Pathophysiology

Pathologically, tissue damage in the form of epidermal necrolysis is a picture of mass keratinocyte cell death through apoptosis. The stimuli that can induce apoptosis include cellular stress, DNA damage and intracellular cytokines.

This apoptosis, as an early marker of EN, may occur from the role of cytotoxic T cells against keratinocytes, through perforin-granzyme B or Fas-Fasl interactions. In 2008, Chung et al provided evidence that there are other cytotoxic molecules that play a role in keratinocyte apoptosis in EN; they are granulysin. Granulysin is a cationic protein, cytolytic that is produced by cytotoxic T lymphocytes, natural killer cells (NK) and natural killer T cells (NKT), found in high concentrations of bull liquid in SJS patients. In addition, recombinant granulysin injection of mouse skins may induce the emergence of EN and inflammatory cell infiltrating.

Another theory of EN pathophysiology is the slow acetylation (drug metabolic disorder) resulting in the increased production of reactive metabolites that are toxic or can trigger a secondary immune response. In addition, there is a hypothesis of the theory of genetic susceptibility, which says there is a strong association between HLA-B75 (allele B * 1502) of HLA-B and HLA-B when EN is caused by carbamazepine and phenytoin, and between HLA-B58 (allele B * 5801) and due to allopurinol in Asians.

A. Role of cytotoxic T cells against keratinocytes

The exact role of cytotoxic cells in drug allergic reactions is unclear. Several major pathways causes the target cell apoptosis by cytotoxic T lymphocytes; perforin-granzyme-mediated exocytosis and Fas-Fasl interactions and action of granulysin role.

1. Perforin-granzyme pathway

The presence of activated T cells that expresses granzyme B (GrB) and perforin has been observed in various immunologic diseases, such as acute heart disease, lungs, and renal allograft rejection. This mechanism is also observed in EN (Figure 1).
GrB and perforin are cytolytic proteins released by activated cytotoxic T cells and NK cells. Perforin creates pores in the cell membranes to allow GrB to enter cells and induce apoptosis by activating the caspase cascade. However, perforin and GrB are present in the vesicles and sent to other cells through the 6-phosphate mannose receptor to cause apoptosis through multiple pathways. The increased numbers of perforins, Granzyme B, α tumour necrosis factor (TNF-α) and FasL has been observed correlated with the severity of drug hypersensitivity disease in both mild and lighter maculopapular eruptions of TEN. In addition, the cytotoxic effects of lymphocytes on keratinocytes can be attenuated by the inhibition of perforin-GrB, but not through the monoclonal antibody anti-Fas.¹³

2. The Interaction of Fas-Fas ligand (Fas-FasL)

FasL is a part of the TNF cytokine and it can induce apoptosis by binding to specific cell surface receptors, that is fas death receptor. Fas function as a cell surface sensors that detects specific extracellular death signals and rapidly triggers cell damage through apoptosis (Figure 2). When FasL binds to the Fas cognitive receptor, apoptotic signals are sent to the cell and further lead to cell disintegration and cell death. In EN, this keratinocyte apoptosis occurs excessively with several hours. Then, apoptosis keratinocytes changes into necrosis and the cohesion between adjacent keratinocytes and keranocyte cohesion to membranocytes and disappear within a few hours to several days. The damaged epidermis determines the degree of EN picture of epidermal necrolysis. This apoptosis can be prevented by monoclonal antibodies that inhibit Fas-FasL interactions.²,¹²

The study of Posadas et al, showed elevated levels of proinflammatory cytokines (TNF-α) and cytotoxic markers (perforin, Granzyme B and FasL) in drug-induced slow hypersensitivity reactions, especially in the acute phase and the levels returned to normal upon resolution. Thus, these cytokines can induce adesi, activate T cells and monocytes and participate in apoptosis.¹²
Figure 2. Death of apoptotic cells through the Fas signal path. Fas and FasL are transmembrane proteins. The Fas signal is induced in contact with the membrane bound to the FasL of adjacent cells. Then, the Fas-associated death domain (FADD) and pro-caspase-8 proteins are released and cause auto-activation of the caspase-8 protease and the apoptosis caused by the activation of the effector caspase (caspase-3, -6, -7) causing disintegration and cell death.\textsuperscript{2,14}

3. Granulysin
Recent research on granulysin, a multifunctional cytolytic protein explains the pathogenic mechanisms underlying extensive keratinocyte death in EN. The level of granulysin is 15-kDa higher than those of perforin, GrB, and FasL in SJS-EN bull fluid. Decreasing the amount of granulysin causes a lack of EN bull liquid cytotoxicity to keratinocytes. In addition, the increase in serum granularin level is obtained at the initial phase of SJS EN but not in patients with drug-induced maculopapular eruptions. Instead of cytotoxic effects, granulysin functions as a chemoattractant for T lymphocytes, NK cells, monocytes, and other inflammatory cells. Based on this discovery, it is hoped that a specific antigranuline therapy for EN will be found in the near future.\textsuperscript{13}

Figure 3 summarizes the current SJS-TEN pathophysiology. In individuals with certain predisposing factors after drug exposure, there is a specific immune response to the drug or one of its metabolites.\textsuperscript{2}

In addition to those mentioned above, various cytokines / chemokines can also cause proliferation and activation of T cells and increase the level of other immune cells in skin lesions, bullae, bullae, peripheral blood mononuclear cells (PBMC) or plasma in SJS-TEN patients. These cytokines include interferon-Ɣ (IFN Ɣ), TNF-α, interleukin-2 (IL-2), IL-5, IL-6, IL-10, IL-12, IL-13, IL-15, IL-18, cell chemokine receptor type 3 (CCR3), chemokine CXC receptor (CXCR3), CXCR4 and CCR10.\textsuperscript{13}

B. N-Acetylation capacity
Low N-acetylation capacity is a predisposing factor for the occurrence of EN in patients requiring drugs containing N-acetylation such as sulfonamides (sulfasalazine), isoniazid (INH), dapsone, hydralazine, procainamide, clonazepam and nitrazepam. Acetylation of these drugs is catalyzed by the N-acetyltransferase (NAT) enzyme encoded by
two genes namely NAT-1 and NAT-2 located on chromosome 8. The NAT-2 locus is the site for determining the genetic polymorphism of the N-acetylation capacity. To date, there are two phenotypes have been identified: slow acetylators and fast acetylators. The fast acetylator phenotype is quickly found in most Eskimos of Canada, Japan or China. In contrast, in Caucasians, slow and fast acetyl distribution differs that is 60% of the population are fast acetylators and 40% are slow acetylators.15

Genetic polymorphism in the N-acetylation phenotype has important clinical relevance in terms of detoxifying carcinogenic substances and in drug metabolism. In particular, the increased frequency of bladder cancer induced by chronic arterial amine exposure (which requires N-acetylation for detoxification) is associated with a slow N-acetate phenotype. N-acetylation polymorphism also has clinical implications of drug metabolism, drug dose and drug side-effects, e.g., fast N-acetylators require higher doses of INH to maintain adequate drug serum levels than slow N-acetylators. Thus, slow N-acetylator phenotypes may be predisposed to adverse reactions of drugs requiring N acetylators.15

C. Genetic Factors
The drug and genetic (pharmacogenomic) relationship with the occurrence of EN can occur through immunological and non-immunological mechanisms.16

1. Pharmacogenomic mediated by immune
Over the past decade, there have been many connections have been established between SJS-EN and the HLA allele of Class I and II major histocompatibility complex (MHC). Several studies have been conducted to explain how small synthetic molecular compounds (drugs) are recognized by T cells dependent on MHC, including the concept of hapten / prohapten model, pharmacological interaction (pi) model, which is pharmacological interaction of drugs with immune receptor and the changed repertoire model. However, the findings cannot be confirmed in Europe. Thus, the risk of EN is associated with high-risk drug exposure and genetic predisposition. For safety purposes, preclinical drugs must be screened to evaluate the interactions between drugs and HLA.6,17

SJS-EN, is associated with impaired ability to detoxify reactive intermediate drug metabolites. This condition is preceded by an immune response to an antigenic complex formed by a metabolite reaction with a particular host tissue. Genetic susceptibility may also play a role, as evidenced by the identification of drug-related HLA alleles as susceptible genes to the development into EN. In addition to the alleles listed in Table 1, HLA-DQB1 * 0601 alleles have been reported in disproportionate numbers in white patients with SJS and ocular complications. This finding shows that these alleles may provide an increased risk for this specific clinical phenotype.2 This observation has important theoretical implications because HLA genes play a role in immune mechanisms. However, given the different associations found in Taiwan compared with other countries, this assumption cannot be applied in other contexts.18

Several hypotheses that explain the interactions between HLA effector cells and drugs have been proposed to explain the immune-mediated mechanism of SJS-TEN, which explains the interactions between HLA-effector cells and drugs, including:

a. Hapten
This hypothesis explains that the drug/metabolite cannot induce an immunogenic reaction. The drug acts as a hapten and forms a covalent bond with the host cell peptide and is then presented by HLA to a T cell receptor in accordance with the classical antigen path of the peptide.

b. Direct pharmacological interaction (P-I)
This hypothesis explains that the drug/metabolite initiates an immune reaction through a reversible and direct interaction with receptors of T cells and HLA containing peptides without the need for prior metabolism of the drug. This direct interaction is evident in the case of carbamazepine-induced SJS which shows that HLA-B * 1502 contains endogenous peptides that bind directly without involvement of intracellular drug metabolism or antigen process pathways.
Table 1. Pharmacogenetic HLA associated with SJS-TEN

| Drugs           | HLA Allel(s)                          | Etnics                      |
|-----------------|---------------------------------------|-----------------------------|
| Alopurinol      | B*5801                                | Han China, Thailand, Korea, Japan, Europe |
| Carbamazepine   | B*1502, B*1511, B*1518, B*5901, C*0704, A*3101 | Han China, India, Europe, Thailand, Korea, Japan |
| Lamotrigine     | B*1502; B*38; B*5801, A*6801, Cw*0718, DQB1*0609, DRB1*1301 | Han China, Japan, Europe |
| Metazolamid     | HLA-B*5901, HLA-CW*0102                | Korea, Japan                |
| Oksikam         | B 73; A*2, B*12                       | Europe                      |
| Okskarbazepin   | B*1502                                | Han China                   |
| Phenytoin       | B*1502                                | Han China, Thailand         |
| Sulfamethoxazole| A*29, B*12, DR7                       | Europe                      |

C. ‘Altered self-repertoire’
Based on this hypothesis, drug bonding with HLA increases the specificity of antigenic bonding loopholes that allow new receptors of endogenous peptides to bind and be presented, resulting in a response of CD8 + alloreactive T cells. A research focused on this hypothesis, one of which abacavir drug hypersensitivity. Abacavir bonding with antigens binding to HLA-B5701 results in stereochemical changes in antigen bonding loopholes.

This alteration inhibits the normal repertoire of peptide bonds and causes a new peptide receptor bond that contains an immunogenic neoepitope. In addition, Illing et al explained that the same process occurs in SJS patients induced by carbamazepine associated with HLA-B * 1502. However, this hypothesis cannot explain what should be considered in clinical practice. The altered self-repertoire hypothesis explains that the drug changes the peptide receptor to each allele carrier (8% of the Han Chinese population has HLA-B * 1502 alleles), but other factors are also needed in this carbamazepine-induced SJS because of its low prevalence of this carbamazepine-induced SJS is low (0.1% of new users) and 7% of carbamazepine users who have this allele are tolerant to carbamazepine, which confirms that another factor is needed in the onset of SJS.11

2. Pharmacogenomics mediated by non-immune
Although predisposing HLA plays an important role in SJS-EN, other factors such as individual differences in clearance or drug metabolism may also contribute to the occurrence of recovery or prognosis EN. Drug cleaning is important to prevent further damage due to drug toxicity retention in the body, drug metabolism to become other forms is key in the occurrence of SJS-EN.16

Impaired drug metabolism is involved in the pathophysiology of SJS-EN, ie the presence of CYP2C locus variants associated with SJS-TEN that was induced by phenytoin. From a genomic association study that included 105 cases of EN-related phenytoin, there have been identified 16 single polymorphic nucleotides that are significant in the CYP2C gene at 10q23.33. This suggested that CYP2C9 * 3 which reduced the CYP2C9 enzyme activity is significantly associated with SSJ-NET induced by phenytoin. In SJS-EN patients induced by phenytoin carrying CYP2C9 * 3, there was a delay of phenytoin clearance in plasma.20 It was known that CYP2C9 * 3 is associated with drug metabolism and may reduce phenytoin clearance.16
Figure 3. Patomechanisms of epidermal keratinocyte apoptosis in SJS and TEN. A number of drugs can trigger widespread keratinocyte apoptosis in the epidermis of SJS or TEN patients that is causing skin to blister and peel. Several theories have been proposed for this condition: (a) the drug may cause an increase in FasL by keratinocytes that constitutively express Fas, which causes apoptosis mediated by death receptors; (B) the drug interacts with cells expressing class I MHC and then drug-specific CD8+ cytotoxic T cells accumulate in epidermal blisters, releasing perforin and granzyme B which is killing keratinocytes; and (C) this drug can also trigger the activation of CD8+ T cells, NK cells and HCV cells to secrete granulysin which causes the death of keratinocytes without contacting with the cell.\textsuperscript{2,19}
In addition, Chung et al have proven that renal insufficiency directly affects the excretion of plasma oxypurinol, the active metabolite of allopurinol, which was primarily eliminated through the kidneys and there was a high level of oxypurinol in patients’ plasma in EN patients induced by allopurinol. Based on the analysis between the allopurinol-induced EN cases and controls, it showed that renal function impairment was significantly associated with allopurinol-induced EN. In addition, it was also found that the levels of oxypurinol in plasma remained high after the cessation of allopurinol. This correlated with prolonged morbidity and skin reactions in ALOpurinol-induced EN. High levels of oxypurinol in plasma could trigger T lymphocytes and then induced a stronger immune response, thus leading to prolonged disease remission, poor prognosis and high mortality rates in EN patients.\textsuperscript{16}

Management

Therapy management of SJS-EN patients requires rapid diagnosis, immediate suspension of suspected drug as soon as possible, and supportive therapy and special therapy (Figure 4). To date, no specific therapy is considered the best for SJS-EN. One aspect of treatment that has a life-saving action in SJS-EN patients is through rapid suspension of drug suspects. The use of special therapies is controversial.\textsuperscript{2,6}

A. Specific Therapy

Immunosuppressive and/or anti-inflammatory therapy is given to stop the disease progression. Neither has proven its effectiveness. The low prevalence of this disease causes randomized clinical trials to be difficult.\textsuperscript{1,2,22}

1. Corticosteroids

The use of corticosteroids is still controversial. Corticosteroids may prevent the extension of the disease when administered during the initial phase, that is given within 72 h since the first onset of symptoms, e.g., by giving intravenous dexamethasone (IV) 1.5 mg/ kg/day for 3 days.\textsuperscript{1,2,23} Therapy with methylprednisolone infusion at 1000 mg/day for 3 consecutive days is also effective. The IV administration 500 mg methylprednisolone on a daily basis (2 days) and 250 mg for 3 days ahead is also effective.\textsuperscript{23} Kim et al administered methyl prednisolone therapy of 250-1000 mg/day in TEN patients and conducted gradually tapering dose with oral prednisolone.\textsuperscript{24,25} Michael et al suggested oral prednisolone tapering dose for 7 - 10 days.\textsuperscript{26}

However, other studies have concluded that steroids fail to stop the progression of diseases and are even associated with increased mortality and side effects, especially sepsis. Specific guidance in the use of systemic corticosteroids varies and will remain variable due to the absence of a controlled trial. Thus, systemic corticosteroids systemic are not recommended as a leading treatment of EN.\textsuperscript{1}

The action mechanisms of corticosteroids in EN occur through the inhibition of epidermal apoptosis by several mechanisms, i.e., inhibiting the action of various cytokines, such as TNF-\alpha, INF-\gamma inhibition that may induce apoptosis and inhibition of Fas-mediated keratinocyte apoptosis.\textsuperscript{26}

2. Intravenous immunoglobulin (IVIG)

Intravenous immunoglobulin (IVIG) can inhibit the Fas-L bond with Fas.\textsuperscript{19} A high dose is recommended, 0.75 g/kg/day for four consecutive days.\textsuperscript{1,2} A high IVIG dose administration will increase life expectancy.\textsuperscript{22} However, IVIG also cannot be standard of therapy because pathways other than Fas-FasL pathway are involved in the occurrence of EN.\textsuperscript{28} Stella et al reported their experience with treating TEN both with and without IVIG. In their report, they treated eight TEN patients with extensive epidermal debridement and coverage with artificial skin substitutes in the pre-IVIG series (patients not treated with IVIG) and treated 23 patients with IVIG (0.7g/kg/day for 4 consecutive days) and conservative wound management in the IVIG series. The IVIG-treated group also received methylprednisolone at doses of 250mg every six hours for the first 48 hours of admission. Cessation of further epidermal detachment from the onset of IVIG therapy averaged five days and complete wound healing occurred after an average of 12.3 days. The average SCORTEN score was 3 in both groups with approximately 35 percent of patients expected to die. The observed mortality was 75 percent and 26 percent in the pre-IVIG and IVIG-treated groups, respectively. In four cases, the cause of death was septic shock and multiple organ failure. Other
causes of death were respiratory failure and disseminated intravascular coagulopathy.²⁹

3. Plasmapheresis or hemodialysis
The use of plasmapheresis or hemodialysis may exclude the drug involved, its metabolites, or inflammatory mediators such as cytokines. Plasmapheresis can be used as an effective adjuvant therapy for SJS patients who are non-responsive to systemic corticosteroids and IVIG, patients with severe clinical complications such as hepatic encephalopathy, and TEN patients who suffer from the disease for more than 70% of the body surface area.

4. Cyclosporine
Cyclosporine is a calcineurin inhibitor that is often used in transplantation and autoimmune diseases. This drug can shorten the complete reepithelization period significantly and upon observation, a limited number of cases malfunctioning organs and death has been reported. The mechanism of cyclosporine action has a great importance in the treatment of EN. As a potent immunosuppressant, cyclosporine in the EN has a biological effect that can inhibit T cell activation and prevent the production of important cytokines in the pathophysiology of EN.³²

Thus, cyclosporine selectively works on immunological changes that trigger keratinocyte death and prevent apoptosis.³² In Mohanty et al’s study, cyclosporine at a dose of 5 mg / kg / day for 10 days from the onset of EN can reduce the risk of death and may speed up lesion healing.³³

B. Supportive therapy
Supportive therapy in SJS-EN is similar to management of burn patients with the aim of avoiding complications, that can lead to death. Complications that can arise include hypovolemia, electrolyte imbalance, renal insufficiency and sepsis. Supportive therapy required includes daily wound care, hydration and nutritional support.²

![Figure 4. Therapeutic approach in SJS-TEN patients.²](image-url)
1. **Wound care**
Wound care is best performed once daily by a dermatologist. Patient mobility should be reduced, because any movement can trigger epidermal release. Skin care is mainly focused on the face, eyes, nose, mouth, ear, anogenital area, armpit folds and interdigital segments. Unaffected areas should be kept dry and not manipulated. The area of the lesion, especially on the back and often under pressure should be reepitlization, but the surface must be cleaned every day with isotonic sterile sodium chloride solution. Another option is to place a large non-adherent dressing pad (eg Exu-Dry™) above the patient and in bed.

For eyes, routine examination by an ophthalmologist is recommended. The eyelids should be gently cleaned daily with an isotonic sterile sodium chloride solution and an antibiotic ointment should be applied to the eyelid. In addition, drip antibiotics should be given to the cornea to reduce colonization of bacteria that can cause scarring. The nose should be cleaned daily with sterile cotton and moistened with an isotonic sterile sodium chloride solution and then the same procedure is used to apply a little antibiotic ointment (e.g., mupirocin). The mouth should be rinsed several times a day using a syringe with an isotonic sterile sodium chloride solution and then aspirated if the patient is unconscious. In anogenital and interdigital areas, daily skin care is applied by applying a silver nitrate solution (0.5%) in the case of maceration or sterile sodium chloride solution. Another option is to use a syringe with an isotonic sterile sodium solution. The area of maceration should be gently cleaned daily with an antibiotic ointment (e.g., mupirocin). The mouth can be used to cover eroded areas. Silicone dressing does not need to be replaced and can be left until and the venous catheter should be placed, if possible, in the uninvolved skin area.

2. **Hydration**
EN is associated with fluid loss through the erosion area, which causes hypovolemia and electrolyte disturbance. Fluid replacement should be conducted as soon as possible and measured daily. SJS patients should be treated in incentive care rooms especially if there is epidermal release of 10%-20% occurs in the body surface area. Measurement of blood pressure, temperature and balance sheet of fluids are needed. Room temperature should be between 29°C- 30 °C (82-86 °F). All patient manipulations should be sterile coated with the albumin vaseline gauze until reepitlization takes place. For the face area, the hemorrhagic and / or serous crusts are cleaned on daily basis with an isotonic sterile sodium chloride solution. Antibiotic ointment (e.g., mupirocin) should be applied to the areas around holes (ear, nose, and mouth) and silicone dressings can be used to cover eroded areas. Silicone dressing does not need to be replaced and can be left until the venous catheter should be placed, if possible, in the uninvolved skin area.

3. **Nutritional support**
Nutritional support is usually given through the nasogastric tube (NGT) to speed up healing and reduce the risk of bacterial translocation of the gastrointestinal tract.

**Conclusion**
SJS and TEN syndromes have a major impact on public health because of their high mortality that occurs. Over the past decade, studies have focused on SJS-TEN pathophysiology, such as the discovery of genetic markers, clarification of HLA interactions and T cell receptors and granulysin identification as a key mediator in epidermal necrosis.

The main therapy of SJS-TEN involves stopping the suspected drug. Other treatments that can be given, such as corticosteroids, IVIG, plasmapheresis and cyclosporine are still controversial. An understanding of the pathophysiology and current management of SJS and TEN is expected to assist in the prevention of disease and early diagnosis and can provide more effective therapy for SJS-TEN treatment.

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