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Stevens-Johnson Syndrome (SSJ) and Toxic Epidermal Necrolysis (TEN)

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Abstract
Stevens-Johnson syndrome (SSJ) and toxic epidermal necrolysis (TEN) are acute, rare, and potentially fatal type IV (Subtype C) skin hypersensitivity reactions that cause skin loss and in some cases may result in loss of mucous membranes followed by systemic symptoms. In general, the incidence of SJS is 1-6 cases/million population/year, and the incidence of NET is 0.4-1.2 cases/million population/year. SJS and TEN are considered to be on the same disease spectrum with different degrees of severity. The exact cause of SJS is currently unknown, but several things have been found that can trigger SJS, such as drugs or viral infections. A collection of symptoms (syndromes) in SJS and TEN in the form of abnormalities characterized by erythema, vesicles, bullae, purpura on the skin at the mouth of the body cavity which has mucous membranes and eyelid mucosa. The success of SJS treatment is largely determined by early recognition of symptoms, stopping or overcoming the causative factors, and providing adequate supportive therapy. A literature review discusses and analyses published information in a particular subject area. Sometimes the information covers a certain time period. Syndrome Stevens-Johnson (SSJ) and nekrolisis epidermal necrolysis (NET) is a hypersensitivity reaction type IV (subtype C) skin that is acute, rare, and potentially fatal cause loss of skin and in some cases can result in its loss of mucous membranes followed by systemic symptoms
Keywords: Stevens-Johnson Syndrome; Toxic Epidermal Necrolysis; SJS; TEN;

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Introduction

Stevens-Johnson syndrome (SSJ) and toxic epidermal necrolysis (TEN) are acute, rare, and potentially fatal type IV (Subtype C) skin hypersensitivity reactions that result in skin loss and in some cases may result in subsequent loss of mucous membranes. systemic symptoms (Fakoya et al. 2018; Oakley and Krishnamurthy 2017; Wang et al. 2019)

Stevens-Johnson Syndrome usually appears shortly after the drug is injected or taken, and the amount of damage caused is sometimes not directly related to the dose but is largely determined by the reaction of the patient's body. Hypersensitivity reactions are very difficult to predict, best known if there is a previous history of the disease and sometimes the patient is not aware of it if the fast type of allergy such as anaphylactic shock if treated quickly the patient will survive and have no sequelae, but if Stevens-Johnson Syndrome will require a long recovery time. long and not immediately cause death such as anaphylactic shock. The mortality rate for SSJ and TEN is quite high, from the available data, the mortality rate in SSJ cases is around 1-5% and in NET cases 25-35%. In connection with the high mortality rate of SJS and TEN cases, comprehensive management is needed, namely rapid diagnosis, rapid identification of the causative drug, treatment in intensive care rooms, and evaluation of prognosis using the severity of illness score for TEN (CORTEN) (Mockenhaupt 2014).

Method

A literature review discusses and analyses published information in a particular subject area. Sometimes the information covers a certain time period.

Result and Discusion

Definition Of SJS And TEN

SJS and TEN are life-threatening diseases (Laun et al. 2016). SJS and TEN are considered to be on the same disease spectrum with different severity (Hasegawa and Abe 2020). Stevens-Johnson syndrome, otherwise known as erythema multiforme major, is considered to represent a series of diseases, the most benign type being erythema multiforme, while toxic epidural necrolysis is the most severe (Smelik 2002). Therefore, SJS and TEN are differentiated based on the large surface area of the detached skin (Oakley and Krishnamurthy 2017).

The acute phase in SJS/TEN patients is characterized by visible rashes and pink to black spots accompanied by pain that can develop into blisters and usually occurs on the skin, lips, mouth, eyes and genitals, the picture is shown in the following picture (Eginli et al. 2017).

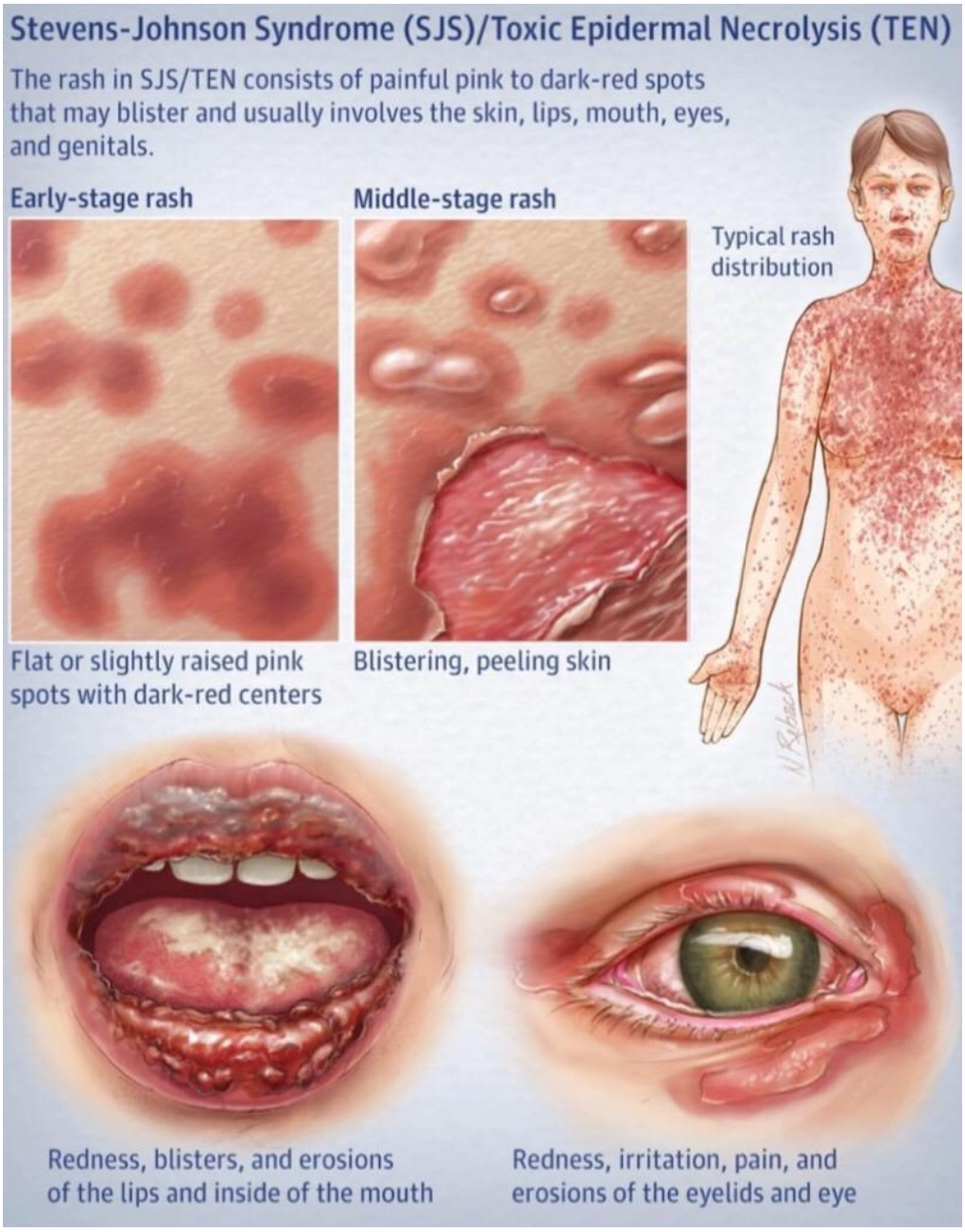

Figure 1. Rash in Steven-Johnson Syndrome and Toxic Epidermal Necrosis

Epidemiology Of SJS And TEN

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis are rare diseases. In general, the incidence of SJS is 1-6 cases/million population/year, and the incidence of NET is 0.4-1.2 cases/million population/year. The mortality rate for NET is 25-35%, while the mortality rate for SJS is 5-12%. This disease can occur at any age, but there is an increased risk at the age of over 40 years. Women are affected more often than men with a ratio of 1.5:1. Data from the RSCM inpatient room showed that in 2010-2013 there were 57 cases with details of SJS 47.4%, SJS-NET overlap 19.3%, and NET 33.3% [2].

Etiology Of SJS And TEN

It is estimated that 75% of the etiology of Stevens-Johnson syndrome cases is drug-related. In addition to drugs, it is reported that infection is an etiologic factor of SJS such as upper respiratory tract infections and Mycoplasma pneumonia infections, as well as diseases such as influenza. In children, Stevens-Johnson syndrome is usually triggered by viral infections, such as mumps, flu, herpes simplex virus, coxsackievirus that causes Bornholm disease, and Epstein-Barr virus (Mockenhaupt 2014). Bacterial infections are less likely to trigger Stevens-Johnson syndrome. In adults, it is often caused by an adverse drug reaction. The drugs most commonly causing Stevens-Johnson syndrome are allopurinol, carbamazepine, lamotrigine, nevirapine, the "oxicam" class of anti-inflammatory drugs (including meloxicam and piroxicam), phenobarbital, phenytoin, sulfamethoxazole, sertraline, and sulfasalazine (Davis and Schafer 2018).

Pathophysiology Of SJS And TEN

Stevens-Johnson Syndrome is an immune complex-mediated hypersensitivity disorder caused by drugs, viral infections, and malignancies. The pathogenesis is unclear, thought to be caused by type III and IV hypersensitivity reactions. Type III hypersensitivity reactions occur due to the formation of micro-precipitation antigen-antibody complexes resulting in complement system activity. As a result, there is an accumulation of neutrophils which then release enzymes and cause tissue damage to the target organ (target organ). This occurs when antigen-antibody complexes circulating in the blood deposit in blood vessels or tissues. Antibiotics are not directed at the tissue but are trapped in the capillary network. In some cases, foreign antigens can adhere to the tissue causing the formation of antigen-antibody complexes at that site. This type of reaction activates complement and mast cell degranulation, resulting in tissue or capillary damage at the site of the reaction. Neutrophils are attracted to the area and begin to metabolize the damaged cells, resulting in the release of cellular enzymes, as well as the accumulation of cell residues. This causes the cycle of inflammation to continue (Kottuvesha n.d.)

Type IV hypersensitivity reaction occurs when the synthesized T lymphocytes re-contact with the same antigen and then the lymphokines are released as an inflammatory reaction. In this reaction mediated by T cells, activation of T cells occurs. Produces lymphokines or cytotoxics or an antigen resulting in the destruction of the cells concerned. This cell-mediated reaction is slow (delayed) requiring 14 to 27 hours to form. In some cases, a skin biopsy may reveal deposits of IgM, IgA, C3, and fibrin, as well as circulating immune complexes. The causative antigen in the form of a hapten will bind to a carrier that can stimulate a specific immune response to form circulating immune complexes. These haptens or carriers can be causative factors (eg viruses, drug particles, or their metabolites) or products arising from the activity of these causative factors (damaged and free cell structures or cell tissues due to infection, inflammation, or metabolic processes). Circulating immune complexes can precipitate in the skin and

mucosa, and cause tissue damage due to complement activation and inflammatory reactions that occur. Tissue damage can also occur due to the activity of T cells and the mediators they produce. Tissue damage that is seen as a local clinical abnormality in the skin and mucosa can also be accompanied by systemic symptoms due to the activity of mediators and other inflammatory products. The presence of a cytotoxic immune reaction also results in keratinocyte apoptosis which eventually causes epidermal damage. Due to the hypersensitivity process, skin damage occurs, such as skin function failure that causes fluid loss, hormonal stress followed by increased insulin resistance, hyperglycemia and glucosuria, thermoregulation failure, immune function failure, and infection (Kottuvesha n.d.).

Clinical Manifestations Of SJS And TEN

Disease begins with nonspecific symptoms such as fever and malaise, upper respiratory tract symptoms such as cough, rhinitis, eye pain, and myalgia. Over the next three to four days, a rash of blisters and erosions appears on the face, limbs, and mucosal surfaces (Oakley and Krishnamurthy 2017). The typical early symptoms of Steven-Johnson syndrome are a productive cough with purulent sputum (phlegm), headache, malaise and arthralgia (Wang et al. 2019). Patients may also complain of a rash with a burning sensation that starts on the face and then moves to the upper body (torso). Skin lesions are characterized as follows:

1. Rash starts from the macula that develops into papules, vesicles, bullae, urticarial plaques, erythema
2. Characteristic lesions that appear on several sites of the target, are considered pathognomonic
3. In contrast to the typical erythema multiform lesion, this lesion has only 2 zones of color
4. The core of the lesion may be vesicular, purpuric, or necrotic with a zone surrounded by erythematous macules
5. The lesion may become bullous and then rupture, leaving the skin denuded and the skin may be susceptible to secondary infection
6. Urticarial lesions not pruritic
7. Infection can cause scarring associated with morbidity
8. Although lesions can occur anywhere, palms, soles, dorsum of hands, but extensor surfaces are most commonly affected
9. Rash may be limited to one area of the body, most often in the central part of the body (torso). Mucosal signs include erythema, edema, ulceration, necrosis, sloughing, and blistering (Wang et al. 2019).

Treatment Of SJS And TEN

The success of the treatment of SJS is largely determined by early recognition of symptoms, stopping or overcoming the causative factors and providing adequate supportive therapy. Detection of the most common causative factors, namely earlier drug

use and immediate discontinuation, has been shown to reduce mortality and improve prognosis. Supportive therapy is an important treatment in SJS patients (Komang Ayu 2019).

Patients who generally present with severe general condition require fluids and electrolytes, as well as parenteral appropriate caloric and protein requirements. Fluid administration depends on the extent of skin and mucosal abnormalities involved. Nutrition through a nasogastric tube is carried out until the oral mucosa returns to normal. Proper care of the skin lesions will reduce the chances of infection and pain. Blisters on the skin can be compressed with saline or borowi solution. Avoid using skin ointments that contain sulfa. Open skin lesions are treated like burns, so coordination with the burn unit is essential. Lesions on the oral mucosa were given mouthwash and glycerin ointment. Pain control with oxicam-NSAIDs should not be given because it is one of the drugs that has been proven to be a frequent cause of SJS (Komang Ayu 2019).

Treatment of secondary skin infections, as initial therapy can be given broad-spectrum antibiotics, can be used gentamicin 5 mg/kgBB/day intramuscularly. Subsequent administration of antibiotics was based on the results of culture and bacterial resistance tests from skin lesions and blood preparations. The selection of antibiotics should not use sulfa and penicillin groups which have a high risk for the occurrence of SJS.

The administration of systemic corticosteroids as a therapy for SJS is still controversial. Some investigators agree on systemic corticosteroid administration arguing that corticosteroids will reduce disease severity, accelerate convalescence, prevent severe complications, stop disease progression and prevent a recurrence. Some literature states that systemic corticosteroid administration can reduce inflammation by improving capillary integrity, stimulating lipocortin synthesis, and suppressing the expression of adhesion molecules. In addition, corticosteroids can regulate the immune response through the down-regulation of cytokine gene expression. Those who do not agree with corticosteroids argue that corticosteroids will inhibit wound healing, increase the risk of infection, mask early signs of sepsis, gastrointestinal bleeding, and increase mortality. Another factor to consider is to have to tapper off 1-3 weeks. If there is no improvement in 3-5 days, then the administration of corticosteroids should be discontinued.

The use of Human Intravenous Immunoglobulin (IVIG) in SJS is also still controversial. Several clinical studies suggest that giving IVIG at a dose of 1 g/kgBB/day for three consecutive days can reduce the progression of SJS disease. IVIG administration will inhibit FAS receptors in the process of Fas-mediated keratinocyte death [8].

The following is the algorithm for managing SSJ and NET:

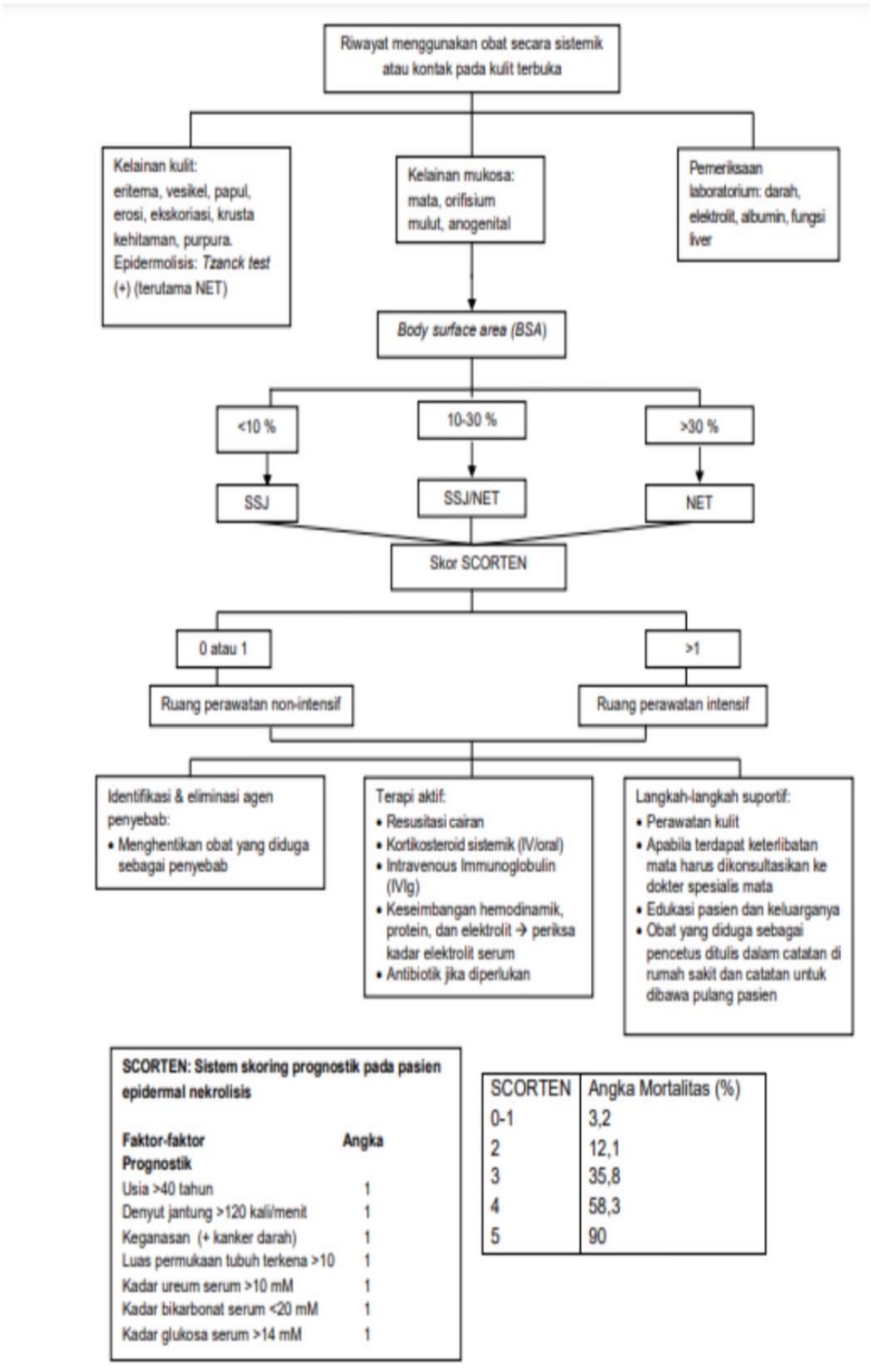

Figure 2. Algorithm for the management of SJS and TEN (Kulit 2017).

Treatment and supportive therapy in SJS-TEN are similar to the 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 therapies needed include daily wound care, hydration, and nutritional support (Diana et al. 2021).

Wound care is carried out with the principle of protecting the exposed viable dermis, minimizing the risk of infection, reducing the risk of pigmentation changes and scarring, and optimizing re-epithelialization. Skin infections and septicemia can be the cause of patient death, so facilitating the healing process can reduce the risk. In particular, infections due to Staphylococcal aureus and Pseudomonas aeruginosa often complicate the clinical course. Irrigation of the wound and intact epidermis can be done with sterile warm water, saline, or dilute chlorhexidine (1/5000). Frequent application of soft emollients such as petrolatum-based products is recommended for the entire skin surface. According to some guidelines, applying a topical antimicrobial agent or dressing impregnated with silver is recommended only for peeling areas of the epidermis.

The ideal dressing should be able to cover all areas of epidermal exfoliation, be absorbent enough to remain attached for several days, have non-adherent properties to minimize trauma during the exchange and be able to prevent infection and biofilm formation. The goals of wound care in SJS/TEN are to minimize physical manipulation of the patient, which can lead to more exfoliation and epidermal pain, and to reduce the frequency of dressing changes while trying to reduce the risk of infection (Jaller, McLellan, and Balagula 2020).

The patient's mobility should be reduced, as any movement can trigger epidermal shedding. Skincare is mainly focused on the face, eyes, nose, mouth, ears, anogenital area, axillary folds, and interdigital segments. Uninvolved areas should be kept dry and unmanipulated. The area of the lesion, especially the dorsal area and which is often under pressure, should be covered with Vaseline albumin gauze until re-epithelialization occurs. For the facial area, hemorrhagic and serous crusts were cleaned daily with sterile isotonic sodium chloride solution (Diana et al. 2021). To prevent contractures, Nano Crystalline Silver (NCS) can be applied with a biological skin substitute. In addition, NCS can be used effectively to support healing and control of pain in disease progression. Nano Crystalline Silver (NCS) is a dressing component that is useful for antibacterial, along with its potential to reduce excessive inflammatory components in disease (Purnamawati et al. 2016). Daily physical therapy should be started as early as possible to maintain limb mobility and increase endurance strength while limiting joint contractures (Shanbhag et al. 2020). In patients with injuries to the back of the hand, after 3 to 4 weeks a rubber band (Figure 3) is used to prevent extensor contractures. Rubber bands were used continuously for 4 to 6 weeks and for 4 weeks only at night, as well as practicing passive/active movements and stretching exercises on the patient (Rrecaj et al. 2015).

Figure 3. Rubber Bands Used to Prevent Contractures.

For the eyes, regular check-ups by an ophthalmologist are recommended. The eyelids should be gently cleaned daily with sterile isotonic sodium chloride solution and an antibiotic eye ointment applied to the eyelids. In addition, antibiotic eye drops should be applied to the cornea to reduce bacterial colonization that can cause scarring.

The nose should be cleaned daily with a sterile cotton swab, moistened with a sterile isotonic sodium chloride solution. The mouth should be rinsed several times a day using a syringe with a sterile isotonic sodium chloride solution, and then aspirated if the patient is unconscious. In the anogenital area and interdigital space, skincare was performed daily by applying silver nitrate solution (0.5%) in case of maceration or sterile sodium chloride solution if no maceration was present. However, there are no standard guidelines for wound care and antibiotic use (Komang Ayu 2019).

Conclusion

Syndrome Stevens-Johnson (SSJ) and nekrolisis epidermal necrolysis (NET) is a hypersensitivity reaction type IV (subtype C) skin that is acute, rare, and potentially fatal cause loss of skin and in some cases can result in its loss of mucous membranes followed by systemic symptoms. The mortality rate for SSJ and TEN is quite high, from the available data, the mortality rate in SSJ cases is around 1-5% and in NET cases 25-35%. The acute phase in SJS/TEN patients is characterized by visible rash and pink to black spots accompanied by pain that can develop into blisters and usually occurs on the skin, lips, mouth, eyes, and genitals. The pathogenesis of SJS/TEN is not fully understood, but it is believed that specific agents (such as drugs and infections) will trigger an immune-mediated cytotoxic reaction against keratinocytes and result in widespread apoptosis, namely the release of epidermal cells from the papillary layer of the dermis at the epidermal-dermal junction, manifesting as papillomacular rash and bullae.

The success of SJS treatment is largely determined by early recognition of symptoms, stopping or overcoming the causative factors, and providing adequate supportive therapy. Detection of the most common causative factors, namely earlier drug use and immediate discontinuation, has been shown to reduce mortality and improve prognosis. Supportive therapy is an important treatment for SJS patients. Treatment and supportive therapy in SJS-TEN are similar to the management of burn patients to avoid complications that can lead to death. Complications that can arise include hypovolemia, electrolyte imbalance, renal insufficiency, and sepsis. Wound care is carried out with the principle of protecting the exposed viable dermis, minimizing the risk of infection, reducing the risk of pigmentation changes and scarring, and optimizing re-epithelialization. To prevent contractures, Nano Crystalline Silver (NCS) can be applied with a biological skin substitute.

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