

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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Since their first descriptions in 1922 and 1948, respectively, Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) have become recognized as manifestations—with different severity—of the same disease process along a spectrum of illness. Even today, decades after their description, there is still disagreement about when a particular bullous disease evolves from erythema multiforme to SJS/TEN. There is no disagreement, however, about the potentially life-threatening nature of the disease. Many cases are misdiagnosed, especially in their early stages. In this paper we address our current understanding of this disease spectrum and discuss both accepted and more controversial modes of therapy.

Introduction

Stevens-Johnson syndrome (SJS) is an immune complex-mediated hypersensitivity disorder. Although some authors believe that SJS is a severe expression of erythema multiforme, others believe that they are separate diseases. SJS is also known as erythema multiforme major. Others use the term *erythema multiforme major* (or *majus*) to refer to severe cases of erythema multiforme major, but differentiate such cases from Stevens-Johnson syndrome. Contributing to the confusion, there is also evidence that toxic epidermal necrolysis (TEN) represents a severe form of SJS, though some still believe that the two are distinct entities. In this article, we assume that SJS and TEN are different manifestations of the same disease continuum.

The skin and mucous membranes are the primary target sites. Significant involvement of oral, nasal, eye, vaginal, urethral, gastrointestinal (GI), and lower respiratory tract mucous membranes may develop in the course of the illness, though minor presentations may also occur. GI and respiratory involvement may progress to necrosis.

SJS/TEN is a serious systemic disorder with the potential for severe morbidity and even death, most commonly due to sepsis or respiratory complications. Misdiagnosis is common in the early stage.

History

Stevens-Johnson syndrome was first described in 1922 with the report of two children, ages 7 and 8, who presented with “an extraordinary, generalized eruption with continued fever, inflamed buccal mucosa and severe purulent conjunctivitis” [1]. TEN was first described by Ruskin in 1948, then again by Lyell in 1956 [2], and was actually referred to as *Lyell’s syndrome* for a time. An association between the development of SJS/TEN and drugs has been established; however, an association with antecedent infection is less clear.

Pathogenesis

The disorder is thought to develop through an immune complex-mediated hypersensitivity process. It is now well-recognized that drugs in various categories are responsible for the development of SJS/TEN. Although the exact mechanism by which the cascade of events that lead to the clinical manifestations has not been fully explained, there are a number of common features. Pathologically, apoptotic keratinocyte cell death causes separation of epidermis from dermis. The death receptor Fas and its ligand FasL have also been linked to keratinocyte apoptosis and dermal-epidermal separation during TEN [3•]. Inflammatory cytokines also have been implicated [4••].

Etiology

Offending agents fall into two broad categories: infections and drugs. Drug-induced cases far outnumber infection-associated cases.

Some authors have suggested that infectious cases are responsible only for erythema multiforme and not SJS. That controversy notwithstanding, infections that have been linked to SJS include *Mycoplasma pneumoniae*, *Yersinia* species, and various *Herpes* species [5,6].



Figure 1. Toxic epidermal necrolysis—lesions of mucous membranes. (From Parrillo and Parrillo [6]; with permission.)

Drugs from several categories have been implicated in both TEN and SJS [6–10]. Some authors distinguish between drugs used on a short-term basis and those used chronically [8]. In the former group, sulfonamides (especially trimethoprim-sulfamethoxazole) are the biggest offenders. Others include aminopenicillins, quinolones, cephalosporins, and chlormezanone. Presentations of SJS/TEN typically occur within 3 weeks of drug exposure.

Drugs used on a chronic basis have also been associated with SJS. These include phenobarbital, phenytoin, carbamazepine, valproic acid, oxcarbazepine, oxicam nonsteroidal (piroxicam, meloxicam), allopurinol, and corticosteroids. There have been reports of SJS in human immunodeficiency virus (HIV)–infected patients treated with the antiretroviral agent nevirapine. Case reports implicating nevirapine include both patients with HIV and individuals receiving the agent for post-exposure prophylaxis [11••]. One author suggests that the problem might extend to other non-nucleoside reverse transcriptase inhibitors [12]. Even with chronic medication use, the greatest risk was seen in the first 2 months after drug initiation.

At-risk Populations

Patients who are HIV-positive, especially those with acquired immunodeficiency syndrome (AIDS), are at high risk for SJS. Whether the disease is an independent risk factor or a function of increased likelihood of drug exposure is still unknown. Intuitively, the latter would make clinical sense. Some have suggested that patients in this group may have abnormal patterns of production or detoxification of drug metabolites; however, other underlying immunologic abnormalities due to HIV may also be operative [11••].

Infection-associated SJS occurs primarily in children, with cases reported in patients as young as 3 months. Children may also develop drug-induced SJS.



Figure 2. Separation of epidermis from dermis in toxic epidermal necrolysis. (From Parrillo and Parrillo [6]; with permission.)

TEN has been associated with graft-versus-host reactions in patients who received bone marrow transplantation [13]. Leukemia, lymphoma, ulcerative colitis, and Crohn's disease have also been named as possible risk factors for TEN [8].

Clinical Presentation

Many patients with SJS/TEN have a prodromal period lasting up to 2 weeks that may include nonspecific signs and symptoms such as fever, chills, headache, sore throat, and malaise. Fever is especially common, occurring in up to 85%. The typical mucocutaneous lesions then develop abruptly, and new lesions may continue to develop for a period of 2 to 4 weeks.

Early lesions are usually erythematous macules with purpuric centers. Unlike typical erythema multiforme lesions, these have only two zones of color: a core, which may be vesicular, purpuric, or necrotic, and a surrounding area of macular erythema. Some investigators have called these “targetoid” in contrast to the three-zone “target” lesions of erythema multiforme [8]. Early macules may evolve into papules, vesicles, bullae, or urticarial plaques. The initial lesions may also appear scarlatiniform. Nikolsky sign (separation of epidermis from dermis with lateral finger pressure) may be easily demonstrated. Areas subject to pressure may demonstrate full detachment (Figs. 1–3).

The distribution of involved areas may be quite variable. In classic cases, lesions begin on the face and upper



Figure 3. Patient with skin sloughing in Stevens-Johnson syndrome. (From Parrillo and Parrillo [6]; with permission.)

torso, with palms, soles, dorsum of hands, and extensor surfaces most commonly affected [6]. The rash may be confined to one anatomic area, most often the trunk. Rash extension usually occurs within 72 hours but may occur over just a few hours.

Any mucosal surface may be affected. Lesions include erythema, edema, sloughing, blistering, ulceration, and necrosis. Oropharyngeal lesions may be severe, but mucosal involvement may also occur on the genitalia, esophagus, and tracheobronchial tree. Lower GI lesions may lead to profuse, protein-rich diarrhea. Erosive vulvovaginitis or balanitis may produce painful genitourinary symptoms. It is important to be aware that internal disease may occur even in the absence of extensive dermal disease.

Ocular involvement may also occur with potential long-term sequelae. Corneal lesions and keratitis are common. Conjunctival erosions may form synechiae in severe cases, and blindness may develop.

Other signs are seen in association with mucosal and organ involvement. These may include fever, orthostasis, tachycardia, hypotension, epistaxis, altered level of consciousness, seizures, and coma.

Classification of Skin Involvement

In 1994 an international group of dermatologists proposed a system of classification by the degree of epidermal detachment [14]. Five categories were developed to encompass the spectrum of disease. 1) Bullous erythema multiforme—detachment of less than 10% body surface area (BSA) plus localized typical target lesions or raised atypical targets. 2) Stevens-Johnson syndrome—detachment of less than 10% BSA plus widespread erythematous or purpuric macules or flat atypical targets. 3) “Overlap” SJS/TEN—detachment between 10% and 30% BSA plus widespread purpuric macules or flat atypical targets. 4) TEN with spots—detachment of more than 30% BSA plus widespread purpuric macules or flat

atypical targets. 5) TEN without spots—detachment of more than 10% BSA with large epidermal sheets but without purpuric macules or targets.

Others have simplified the classification as follows. SJS—a “minor form” of TEN—would be diagnosed when there is less than 10% BSA detachment. Overlapping SJS/TEN cases are represented with detachment of between 10% and 30%, whereas detachment of more than 30% BSA represents classic TEN.

Diagnosis

Although the diagnosis is usually clinically apparent, the differential diagnoses of staphylococcal scalded skin syndrome and other blistering diseases must be ruled out. Biopsy of involved areas can provide definitive discrimination between these processes. Full-thickness epidermal necrosis is consistent with TEN. Other microscopic features include perivascular lymphocyte infiltration [8].

Although no other studies help establish the diagnosis, most investigators recommend routine laboratory studies to include complete blood cell count, creatinine and electrolyte levels, and cultures as clinically indicated. Chest radiography should be done when co-existent pneumonia is suspected. Other diagnostic studies that may be indicated include bronchoscopy, esophagogastroduodenoscopy, and colonoscopy, depending on the extent of involvement.

Treatment

The primary initial concern is volume status. Fluid replacement follows standard guidelines, such as the Parkland formula ordinarily used for burn patients. Estimates of body surface involvement should be done carefully. Large quantities of saline may be required, but characteristically less than would be required in a true burn patient with equivalent BSA involvement. For adults, fluid resuscitation to maintain a urinary flow of 50 to 100 mL/h would be reasonable. In children, the goal is a flow of approximately 1 mL/kg/h.

Most authorities strongly advocate transfer to a burn center if possible, which has been shown to reduce mortality. Owing to the likelihood that even a case that initially appears minor and benign may evolve quickly, many advocate hospitalization for all patients with SJS/TEN [8].

Protein loss can be significant. Nutritional support is critical, and the patient may require parenteral or enteral hyperalimentation.

Whether treated at a burn center or another type of facility, sterile wound care is also critical. Most authorities believe that necrotic tissue must be debrided regularly and replaced with biologic grafts or porcine xenografts. Others leave necrotic intact epidermis in place. One commonly used topical burn treatment—silver sulfadiazine—must be avoided because of its sulfa base.

Although most authors believe that antibiotics should only be used for specific infectious complications, others disagree and recommend prophylactic antibiotics after obtaining cultures in patients with extensive involvement [15••,16].

An ophthalmologist should see all patients with SJS/TEN. Selected patients should also be seen in consultation by a pulmonologist and/or a gastroenterologist if involvement of these organ systems is suspected.

Withdrawal of suspected offending drugs is critical. Doing so earlier rather than later has been shown to decrease mortality rate [17].

Although to date there have been no randomized controlled trials of corticosteroid use, most uncontrolled studies have shown an increased rate of sepsis-related death. It should be noted that although both treated and nontreated patients develop sepsis, those receiving steroids are more likely to die [18].

Most studies show a benefit from the administration of intravenous immune globulin (IVIg). The rationale proposes that IVIg blocks target cell death via a receptor-ligand blocking antibody present in pooled human IVIg [3•,4••]. In an opposing view based on a small prospective study, Bachot et al. [19] stated that their results “do not support the routine use of IVIg treatment for patients with SJS or TEN, especially in cases of impaired renal function.”

In a small uncontrolled study of severe TEN cases (BSA 83% ± 17%), Arevalo et al. [20] showed that patients benefited from cyclosporine when compared with historical controls who received cyclophosphamide and steroids. Given the poorer prognosis in patients receiving steroids, the perceived benefit from cyclosporine is uncertain.

Mortality

Generally speaking, the mortality rate is determined largely by the extent of skin sloughing [3•,8], as follows: less than 10% BSA, 1% to 5%; greater than 30% BSA, 25% to 35%.

The SCORTEN (ie, score for TEN) is a severity-of-illness score, calculated within the first 24 hours of admission [21]. Each feature is assigned one point. The total is the SCORTEN number. Variables include age older than 40 years; presence of malignancy; heart rate greater than 120; initial percentage of skin detachment greater than 10% BSA; blood urea nitrogen (BUN) greater than 10 mmol/L (27 mg/dL); serum glucose greater than 14 mmol/L (252 mEq/L); and bicarbonate less than 20 mmol/L (20 mEq/L).

Mortality based on SCORTEN number is as follows: 0 to 1, 3.2%; 2, 12.1%; 3, 35.3%; 4, 58.3%; 5 or higher, 90%.

Conclusions

Stevens-Johnson syndrome and toxic epidermal necrolysis most likely represent different degrees of severity of the same disease process. Skin and mucous membranes are the primary targets. Early diagnosis and management are key to positive outcomes. Referral to a burn center is warranted if such facilities are available. Fluids and maintenance of nutritional status represent the mainstays of early management. Although still somewhat controversial, many advocate use of IVIg, and cyclosporine is also commonly used. Most avoid corticosteroids because of an attendant increased risk of infection. Careful assessment of the extent of epidermal detachment and other clinical features can provide important early prognostic information. Mortality remains high in patients who have significant areas of skin involvement, with death usually resulting from sepsis or airway compromise.

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