

Outpatient Management of Stevens-Johnson Syndrome: A Report of Four Cases and Management Strategy

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ABSTRACT

Stevens-Johnson syndrome is a severe form of erythema multiforme with or without bullous lesions. This is a potentially life-threatening condition that has traditionally required hospitalization for optimal management. We report the successful management of four patients who developed this syndrome following administration of antimicrobial agents. In our experience, for individuals with mild to moderate disease, Stevens-Johnson syndrome can be managed with corticosteroids as an outpatient. (Allergy and Asthma Proc 18:29–32, 1997)

Erythema multiforme is an acute erythematous maculopapular eruption characterized by the presence of target lesions.¹ The clinical course of this syndrome may progress from a mild, self-limited cutaneous eruption to a severe form with mucosal lesions, visceral organ involvement, and systemic toxicity (Stevens-Johnson syndrome). Some investigators use the term toxic epidermal necrolysis to identify the most severe cases, with severe cutaneous lesions simulating third degree burns.^{2,3} Due to a lack of a precise definition, there is some confusion in the literature regarding the pathogenesis, natural history, and treatment of this syndrome. We consider Stevens-Johnson syndrome (SJS) to be a severe form of erythema multiforme manifested by extensive skin involvement and ulcerative lesions of at least one mucosal surface or visceral involvement or both.^{4,5}

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Stevens-Johnson syndrome is relatively uncommon, accounting for 0.1–0.01% of all hospital admissions. The most common causes of this condition are infections and medications, especially antimicrobial agents. Erythema multiforme is most frequently reported in association with *Mycoplasma* or herpes simplex virus⁶ infections, although other etiologies such as *Histoplasma*, adenovirus, and systemic bacterial infections have been implicated.^{1,3,7–9} Penicillins, cephalosporins, and sulfonamides are the antibiotics commonly associated with SJS.^{1,5,9} Recently, case reports have also identified didanosine,¹⁰ fluconazole,¹¹ and ciprofloxacin¹² as medications resulting in erythema multiforme.

The reported mortality rate with SJS ranges from 30–60% and varies based on severity.¹³ The use of corticosteroids remains controversial,¹⁴ although in our experience it may be life-saving.^{4,5,15} Due to the potential for systemic toxicity and no standardized approach to management, patients with SJS are generally admitted to the hospital for supportive care. We report our experience with the outpatient management of four patients with SJS due to antimicrobial agents.

CASE REPORTS

Case 1

A 39-year-old woman developed an infection in her foot in September 1994, was treated with penicillin, and had a subsequent penicillin reaction manifested by a maculopapular dermatitis. This was treated with an injection of corticosteroids with symptomatic improvement.

In October 1994, she received amoxicillin and developed a generalized dermatitis. This was treated with intermittent methylprednisolone with uncertain improvement. She was seen by at least three physicians and treated with antihistamines, antidepressants, and a variety of topical and other medications with minimal improvement.

The dermatitis progressed to a total body erythroderma with significant edema, particularly of the face. The patient was very uncomfortable and discouraged. She had no bullous lesions of the skin nor mucosal involvement, but visceral involvement demonstrated by liver function abnormalities (LDH 523 IU/L, AST 79 IU/L, and ALT 84 IU/L) and renal involvement demonstrated by microscopic hematuria; however, her serum creatinine was normal.

In the absence of other diagnoses and two adverse reactions to penicillins preceding the problem, the patient was treated for Stevens-Johnson syndrome. She was not acutely ill, so management was initiated on an outpatient basis with 60 mg of prednisone daily. Within 1 week, her clinical symptoms improved and prednisone was changed to 80 mg on alternate days. Reduction of prednisone dosage was conducted on a weekly basis, but when the taper occurred too rapidly, her clinical abnormalities recurred. Thus, a very slow reduction of prednisone was required over a period of 5 months. Following discontinuation of corticosteroid therapy, the patient has remained well and feels completely normal.

Case 2

A 37-year-old man was treated with trimethoprim-sulfamethoxazole. Three days later, he developed generalized urticaria, which progressed to a severe maculopapular rash over the next 24 hours. He made three successive trips to the emergency department, and was treated with antihistamines and moderate dose prednisone (40 mg) without control. His symptoms progressed to severe tongue swelling, oral ulcerations, and worsening conjunctivitis. He was extremely uncomfortable because of arthralgia and dysphagia. He refused hospitalization, so treatment was initiated as an outpatient. He was treated with prednisone 60 mg daily and hydroxyzine with close telephone contact. His symptoms improved on this regimen and he was converted to prednisone 80 mg every other day after 1 week. Progressive reduction of alternate day prednisone was continued, but relatively rapid tapering resulted in symptoms of extreme fatigue. After 2 months, the prednisone was decreased to 25 mg every other day without complications. At this time he left the country for Japan, where further reduction in prednisone was to be carried out. At the time of his departure, his physical examination and laboratory evaluation were normal.

Case 3

A 76-year-old woman, with corticosteroid-dependent asthma for 28 years, required prednisone 25 mg on alternate days for control of her symptoms. She had been highly opposed to prednisone, although it was essential to prevent fatal asthma. She was treated with trimethoprim for 10 days for a urinary tract infection and 2 weeks later developed generalized pruritis, urticaria, periorbital edema, conjunctivitis, and erythema. Her primary care physician admitted her to the hospital for 24 hours, administered

intravenous corticosteroids, and referred her to Northwestern for additional management.

On physical examination, she had periorbital edema, erythema of the conjunctivae, and a generalized severe maculopapular eruption. Her hepatic and renal function were normal. She was treated with prednisone 100 mg daily (in divided doses) as an outpatient with a conversion to lower doses and alternate day therapy over a period of 4 weeks. Although the patient had "prednisonephobia," the diagnosis of SJS made her "prednisonephilic" thereby resisting reduction in prednisone after being alerted to the potential danger of SJS. She was completely controlled with prednisone, which was reduced to 25 mg on alternate days with complete recovery from SJS. After return to her baseline prednisone dose, she again became prednisonephobic and resisted use of inhaled corticosteroids.

Case 4

A 35-year-old man with HIV-1 infection presented to the outpatient HIV center complaining of skin rash, oral ulcers, and conjunctivitis for 6 days. He was currently enrolled in an investigational trial using delavirdine for the treatment of asymptomatic patients. His course had been complicated by a mild skin rash, but according to the study protocol, patients were to continue on therapy despite the rash. There had been no preceding bacterial or viral illnesses. Associated symptoms included low-grade fever and chills. He was on no other medication and had no known allergies.

On physical examination, he was afebrile with normal vital signs. He had a diffuse, pruritic, erythematous maculopapular rash over his entire body. His conjunctivae were mildly injected and there were several erythematous-based ulcerative lesions on his buccal mucosa, soft palate, posterior pharynx, and lips. There was mild hepatomegaly without splenomegaly. The remainder of the examination was unrevealing. Laboratory evaluation was unremarkable except for a lactate dehydrogenase of 292 U/L.

The patient was diagnosed with Stevens-Johnson syndrome and hospitalization was recommended. He refused admission; therefore, treatment was initiated as an outpatient. He was instructed to stop the delavirdine and given oral prednisone 80 mg. He returned for daily evaluations for 3 days and within 72 hours, he had marked improvement in the skin rash. The mucosal lesions also showed improvement and prednisone was decreased to 60 mg daily. The oral ulceration resolved after 7 days of therapy and the prednisone dose lowered to 40 mg daily for another week. Prednisone was then continued at a dose of 20 mg for another 4 days, then 10 mg for 4 days before discontinuation. He remains clinically well without recurrence of his symptoms.

DISCUSSION

The clinical features and outcome of these four patients with SJS treated as outpatients are detailed in Tables I and II. The pathogenesis of this syndrome is not completely under-

TABLE I

Characteristics of Patients with Stevens-Johnson Syndrome Treated as Outpatients

Patient Sex, Age	% Skin Involvement	Bullous Lesions	Mucosal Involvement	Visceral Involvement	Drug	Days before Corticosteroid	Initial Dose of Corticosteroids
1. 39/F	100	none	none	kidney, liver	PCN, amox	60	prednisone, 60 mg/d
2. 37/M	60	none	eyes, mouth	liver	TMP/SMX	2	methylprednisolone, 125 mg
3. 76/F	60	none	eyes	none	TMP	1	prednisone, 60 mg/d
4. 35/M	100	none	eyes, mouth	none	delavirdine	6	prednisone, 80 mg/d

PCN-penicillin; TMP-trimethoprim; TMP/SMX-trimethoprim-sulfamethoxazole; amox-amoxicillin

stood, but it is believed to be immunologically mediated.⁵ This is supported by an association between HLA B15 and erythema multiforme and between HLA B12 and Stevens-Johnson syndrome and toxic epidermal necrolysis.¹⁶ The histopathologic findings also suggest alterations in immune regulation. Initially, in patients with erythema multiforme, skin biopsy reveals a predominantly mononuclear cell infiltrate and basophils around dermal blood vessels, which may indicate a role for cell-mediated immunity in the pathogenesis.¹⁷ In addition, IgM and C3 can be identified in the dermal blood vessels along the dermal-epidermal junction.¹⁸ Finally, the clinical manifestations and immunopathogenesis of graft-versus-host disease and SJS are quite similar.¹⁹

The use of corticosteroids in the management of SJS remains controversial in the literature²⁰; however, in our experience, corticosteroids hasten recovery and may be life-saving.^{5,15} The presumed mechanism of action with

corticosteroids is suppression of the inflammatory response which results from an immunologic hypersensitivity reaction.⁵ While there is no standard type or dosage of these agents, an adequate dose should be administered to exert a significant anti-inflammatory effect. This is especially true in the ambulatory setting, where continuous observation of the patient does not occur (Table III). Corticosteroids should be continued at the initial dose until improvement in symptoms begins and then gradually tapered according to the patient's symptoms. As evidenced by our first patient, if tapering occurs too rapidly, disease activity may flare. Out-patient management should only occur in patients capable of returning for frequent visits and with good support services at home should their condition deteriorate.

As evidenced by our patients, early recognition of SJS is important to optimize management. The first patient had a known hypersensitivity reaction to penicillin, yet was treated

TABLE II

Outcome of Patients Treated with Corticosteroids as Outpatients

Patient	Effect of Corticosteroids	Controversial Issues	Outcome	Comments
1.	Control and induction of remission	Four physicians were unable to properly diagnose	Resolved	Very prolonged course requiring slow reduction of prednisone. Developed syndrome that occurs after some SJS episodes. ²²
2.	Control and induction of remission	Three emergency room visits before diagnosis and management initiated	Controlled (left U.S. on prednisone 20 mg; further taper ongoing)	Two months of continuous reduction of prednisone required because more rapid reduction resulted in exacerbations.
3.	Control	Admitted to another hospital with no diagnosis	Resolved	Patient had corticosteroid dependent asthma, SJS occurred on prednisone, 25 mg QOD, but responded to higher doses. Patient is afraid of prednisone, except when she developed SJS when she developed "prednisonephilia," and did not want to reduce it too rapidly.
4.	Control	Continued delavirdine despite worsening rash	Resolved	Due to high incidence of cutaneous reactions in HIV-1 infected patients and due to this investigational agent, protocol recommends continuation.

TABLE III

Management Strategy for Patients with Stevens-Johnson Syndrome

Clinical Characteristics		Treatment
Mild-moderate	Mild-moderate cutaneous, mucosal, and visceral abnormalities	<i>Outpatient:</i> 60–80 mg prednisone daily Daily contact with patient Taper and begin alternate day prednisone after one week (if symptoms improving)
Severe	Bullous lesions, severe eye involvement, and multiple viscera involved	<i>Admit:</i> Solumedrol 60–80 mg IV every 4–6 hours Consider consultation

with amoxicillin, which resulted in a generalized dermatitis. The second patient developed SJS following exposure to trimethoprim-sulfamethoxazole, one of the most commonly implicated antibiotics. The third patient's problem followed administration of trimethoprim. Our fourth case emphasizes the importance of careful monitoring of investigational antimicrobial agents in HIV-1 infected individuals. Patients infected with HIV-1 are at a greater risk for many cutaneous reactions, including SJS.^{21,22} Adverse reactions to sulfonamides may occur 100 times more frequently in patients with HIV-1 compared to uninfected individuals.²⁰ An interesting aspect of delavridine is that rash occurs commonly with the initial administration of this antiviral agent, but usually resolves several days into therapy. Our patient continued his medication as instructed until SJS was diagnosed.

An interesting aspect of Patient 3 is that SJS developed while on alternate day prednisone for asthma, confirming that no definite recommendation regarding dosing can be made, other than enough to suppress the inflammatory response. In our experience, this is usually 60–80 mg a day of prednisone.

In summary, SJS is a potentially life-threatening syndrome that requires prompt recognition for optimal management. Although many patients have systemic toxicity requiring hospitalization, outpatient management may be possible in those with mild to moderate symptoms. We recommend that if outpatient management is initiated, prednisone 60–80 mg a day is initiated and the patient is followed closely to ensure an adequate anti-inflammatory effect. As symptoms improve, therapy can be gradually tapered until resolution. If patients do not respond or symptoms progress while on therapy, hospitalization may be necessary.

REFERENCES

- Elias PM, Fritsch PO. Erythema multiforme. In: Fitzpatrick TB, Eisen AZ, Wolff K, et al., (Eds.) *Dermatology in General Medicine*. 2nd Ed. New York, NY: McGraw-Hill International Book Co; 1979, pp 295–303.
- Orfanos CE, Shaumburg-Lever G, Lever WF. Dermal and epidermal types of erythema multiforme. *Arch Dermatol* 109:682–688, 1974.
- Lyell A. Mycoplasma and erythema multiforme. *Lancet* 2:1116–1118, 1967.
- Patterson R, Dykewicz MS, Gonzales A, et al. Erythema multiforme and Stevens-Johnson syndrome: Descriptive and therapeutic controversy. *Chest* 98:331–336, 1990.
- Patterson R, Miller M, Kaplan M, et al. Effectiveness of early therapy with corticosteroids in Stevens-Johnson syndrome: Experience with 41 cases and a hypothesis regarding pathogenesis. *Ann Allergy* 73:27–34, 1994.
- Detjen PF, Patterson R, Noskin GA, Phair JP, Loyd SO. Herpes simplex virus associated with recurrent Stevens-Johnson syndrome. A management strategy. *Arch Intern Med* 152:1513–1516, 1992.
- Ström J. Febrile mucocutaneous syndromes in adenovirus infection. *Acta Derm Venereol (Stockh)* 47:281–286, 1967.
- Sellers TF. An epidemic of erythema multiforme and erythema nodosum caused by histoplasmosis. *Ann Intern Med* 62:1144–1162, 1965.
- Shelly WB. Herpes simplex virus as a cause of erythema multiforme. *JAMA* 201:153–156, 1967.
- Parneix-Spake A, Bastuji-Garin S, Levy Y, et al. Didanosine as probable cause of Stevens-Johnson syndrome [letter]. *Lancet* 340: 857–858, 1992.
- Gussenhoven MJ, Haak A, Peereboom-Wynia JD, van't Wout JW. Stevens-Johnson syndrome after fluconazole [letter]. *Lancet* 338:120, 1991.
- Win A, Evers ML, Chmel H. Stevens-Johnson syndrome presumably induced by ciprofloxacin. *International J Dermatol* 33:512–514, 1994.
- Ramussen JE. Erythema multiforme in children: response to treatment with corticosteroids. *Br J Dermatol* 75:181–186, 1976.
- Heimbach DM, Engrav LM, Marvin JA, Harmar TS, Grube BJ. Toxic epidermal necrolysis: a step forward in treatment. *JAMA* 257:2171–2175, 1987.
- Cherian S, Patterson R, Greenberger PA, Grammer LC, Latall J. The outcome of Stevens-Johnson syndrome treated with corticosteroids. *Allergy Proc* 16:151–155, 1995.
- Soter NA, Wuepper KD. Erythema multiforme and Stevens-Johnson syndrome. In: Samter M et al. (Eds.) *Immunological diseases*, 4th ed. Boston: Little, Brown and Co., 1988.
- Tonnesen MG, Harist TJ, Wintroub BU, et al. Erythema multiforme: Microvascular damage and infiltration of lymphocytes and basophils. *J Invest Dermatol* 80:282–286, 1983.
- Huff JC, Weston WL, Tonnesen MG. Erythema multiforme: A clinical review of characteristics, diagnostic criteria, and causes. *J Am Acad Dermatol* 8:765–775, 1983.
- Fischer JLM, Deeg HJ. Graft-versus-host disease. *N Engl J Med* 324:667–674, 1991.
- Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med* 331:1272–1284, 1994.
- Coopman SA, Johnson RA, Platt R, Stern RS. Cutaneous disease and drug reactions in HIV infection. *N Engl J Med* 328:1670–1674, 1993.
- Porteous DM, Berger TG. Severe cutaneous drug reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) in human immunodeficiency virus infection. *Arch Dermatol* 127:740–741, 1991. □



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