

# Potential Adverse Effect Steven Johnson Syndrome with Supplemental Berberine Use

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**Abstract** Steven-Johnson Syndrome is a rare adverse skin reaction, which may progress to critical conditions. The presentation of SJS is a widespread, type-IV hypersensitivity, skin reaction typically induced by infection and numerous medications which occurs approximately 12 hours after exposure to infection or medication. Patients typically initially present with fever, headache, and general malaise. In these patients, within 4 days to 4 weeks [1] of causative medication usage, a diffuse rash develops. Severe cases of SJS can place the patient in critical condition. Complications of SJS can include bacterial infection, excessive fluid loss from denuded skin (or loss of epidermis), hypovolemic shock, or septic shock. [1] Prompt diagnosis and immediate discontinuation of medication is essential to prevent life threatening complications. Herein, we document a case of a patient presenting to the Emergency Department (ED) three days prior to follow up in our office with bilateral leg rash for which the ED prescribed hydrocortisone cream. Upon examination in office, the erythematous eruption had spread to the entire body including her palms. She had started the herbal supplement berberine a month prior to the initial presentation of the rash. Upon cessation of the berberine and completion of a Medrol dose pack, the rash resolved.

**Keywords:** *Steven-johnson syndrome, rash, Berberine, supplements, adverse effects, exposure*

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## 1. Case Presentation

Patient is a 59-year-old female with a past medical history of hypertension and Diabetes Mellitus Type 2. She presented to our primary care clinic with a pruritic and diffuse red macular rash covering her entire body. A month prior to the onset of the rash, the patient was having recurrent fevers. Consequently, she went to an urgent care provider who prescribed Zithromax (Z-pack). Three weeks later, she first noticed the bilateral leg rash and went to the ED. The physician placed her on triamcinolone, a topical corticosteroid, to reduce inflammation and swelling of the skin. However, due to financial constraints, she chose instead to use an over-the-counter hydrocortisone cream, which did resolve the rash briefly. Yet, the following day, she noticed swelling of both of her legs, with the rash reappearing on the posterior aspect of both of her legs. By the next day, the erythematous macular rash had spread diffusely, after which she went to the ED and was screened for syphilis which was negative. She was placed on Prednisone and Clindamycin with no improvement. Upon presentation to our clinic after her discharge, the patient reported taking

Berberine over the past month, beginning around the time the rash appeared. Patient denied any changes in detergents, body wash or new soaps. The patient was advised to discontinue the Berberine supplement and metformin. She was provided Solu-Medrol 125mg IM injection and prescription for 8 mg Medrol Dosepak.

## 2. Background

Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are subtypes of acute mucocutaneous conditions [1]. SJS is a condition that is immunologically mediated by a type IV hypersensitivity. This type of hypersensitivity reaction is a delayed type of reaction where a specific drug or infection activates cytotoxic T cells that target and damage keratinocytes. The presentation can have two phases, beginning with nonspecific symptoms such as fever, headache, myalgia, general malaise, cough, and rhinitis. The second phase develops over the next three to four days, as a diffuse skin rash, appearing on the face, trunk, limbs and mucosa [1]. The rash itself is described as erythematous, targetoid, annular or purpuric macules with blisters and skin detachment (positive Nikolsky sign). Nikolsky sign is the separation of the skin,

specifically the epidermis, upon applied pressure. SJS and TEN can be classified by the extent of skin detachment on a surface area coverage [2]: Stevens-Johnson Syndrome: body surface area <10%, Overlap of SJS/TEN: body surface area between 10% - 30%, or Toxic Epidermal Necrolysis: body surface area >30%.

The score assessment that evaluates the severity of the condition is known as SCORTEN [2,3]. This assessment is typically done within the first 24 hours of presentation and repeated on day 3. The factors taken into account are as follows: Age >40 years, heart rate > 120 beats per minute, skin detachment involving body surface area >10%, blood urea nitrogen >28 mg/dL, blood glucose >252 mg/dL, and bicarbonate <20 mEq/L. The greater the number of risk factors, the greater the mortality rate (seen in Table 1) [3].

Table 1.

Number of risk factors	Mortality rate
0-1	3.2%
2	12.1%
3	35.3%
4	58.3%
>5	90%

The most common etiology of SJS is due to medications, approximately related to over 80% of cases [2]. The most well-known drugs include antibiotics, antiepileptics, allopurinol, and nonsteroidal anti-inflammatory drugs. Certain genetic factors can also have a role in increasing the risk of drug reactions such as cytochrome P inhibition and its role in drug metabolism. Depending on the type of medication, the clearance of the drug can be delayed leading to toxic levels that can increase the risk of adverse effects.

Berberine is an isoquinoline quaternary alkaline bioactive compound found in turmeric tree (*berberis aristata*), barberry (*Berberis vulgaris*), oregon grape (*Berberis aquifolium*) with an extensive use as an herbal supplement in traditional Chinese and Ayurvedi medicine. The usage of Berberine dates back 3000 years. The oldest evidence of its use is as a "blood purifying agent" [4]. In Ayurveda, Berberis has been used for the treatment of infections, wound healing, indigestion, and vaginal disorders. Most recently, it has been studied to be used as a dietary supplement to reduce obesity and as an additive to improve insulin resistance in type 2 diabetes mellitus [8]. In a study conducted by Liu W et al, berberine was shown to decrease levels of malondialdehyde (MDA), which is a marker for lipid peroxidation, as well as increase levels of superoxide dismutase (SOD). Due to its antioxidant properties, berberine has additionally been shown to improve renal function in a patient with diabetic nephropathy [5,8]. Yin Jun et al determined the efficacy of berberine in the treatment of type 2 diabetic patients; the study showed the hypoglycemic effect of berberine to be comparable to the effect of Metformin, a first-line antidiabetic medication, as it lowered the HbA1c significantly along with lowering cholesterol levels [6].

Furthermore, berberine has been shown to have a role in immunomodulation. One of its immunomodulatory roles is acting as a suppressor of Immunoglobulin E production [1]. Secondly, McCubrey J et. al mentions inhibitory interactions berberine has with cytochrome

P450 enzymes (CYP) and thus slowing down drug metabolism [7]. The side effects seen with usage of Berberine include gastrointestinal complaints including, diarrhea, constipation, flatulence, and abdominal pain [9]. To our knowledge, this is the first case reported of berberine usage associated with SJS as a side effect.

### 3. Treatment and Management

The patient was provided Solu-Medrol 125mg IM injection in the office and prescribed 8 mg Medrol Dosepak. She discontinued the Metformin and Berberine with resolution of rash within 10 days. She was restarted on Metformin 1 month later without the recurrence of rash.

### 4. Discussion

The most commonly observed medications to cause SJS are antibiotics, antiepileptics, allopurinol, and nonsteroidal anti-inflammatory drugs [2]. In this case, we present a supplement, Berberine, that may not only have increasing usage in the general population as an herbal supplement, but also may cause an interaction that can lead to SJS in certain patients.

Although the pathophysiology in this reaction is not defined, we propose the possibility of a downstream tyrosine kinase inhibition leading to skin desquamation, ultimately, TEN or SJS [10]. Here we are suggesting that combination of metformin, MAPK pathway inhibitor, coupled with Berberine, a cytochrome P inhibitor, may lead to this lethal skin reaction [11]. It is important to note that metformin is metabolized by cytochrome P, thus in combination with Berberine, will have increased amount of active drug in the body. [12] Thus, the increase metformin and enhance MAPK kinase inhibition, downstream to tyrosine kinase, increasing desquamation of the skin.

### 5. Conclusions

In conclusion, SJS is a critical adverse hypersensitivity reaction where it is imperative to recognize to prevent life threatening complications. There are innumerable medications that have been observed to have an adverse hypersensitivity reaction such as SJS and the list only continues to grow. In our case, we suggest that Berberine is may be a causative agent for the patient developing a diffuse, erythematous rash throughout her body. It is important to have herbal supplementation, specifically Berberine, as a high clinical index of suspicion due to the potentially fatal side effect profiles and rapid deterioration that can occur.

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