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# Fatal case of cephalexin-induced toxic epidermal necrolysis

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**Abstract**

**Purpose:** To describe a case of toxic epidermal necrolysis likely caused by cephalexin with a review of the literature.

**Case:** An 80-year-old male with a known allergy to cephalosporins, residing at a long-term acute care hospital, received cephalexin for a urinary tract infection. And 1 day after starting therapy, the patient developed an extensive erythematous rash accompanied by skin sloughing; 4 days after receiving cephalexin, the patient was directly admitted to the burn intensive care unit and was diagnosed with toxic epidermal necrolysis involving 56% of the total body surface area. Progressive deterioration to multisystem organ failure ensued, and the patient died 5 days following his admission to the burn intensive care unit. At the time of death, ulcerations were noted over approximately 80% of his body.

**Summary:** The temporal association of the patient's ingestion of cephalexin for a urinary tract infection to his onset of toxic epidermal necrolysis suggests that this 80-year-old man developed toxic epidermal necrolysis following the administration of cephalexin for a urinary tract infection.

**Keywords**

Stevens–Johnson syndrome, drugs, allergic reaction, rash

## Introduction

Based on histopathology, most clinicians consider Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) as different severities of the same potentially fatal mucocutaneous disease within the spectrum of erythema multiforme major (EMM).[1] While no widely accepted clinical and diagnostic criteria exist to differentiate SJS and TEN, an often referenced scheme from an international panel of experts is used.[2] The panel suggests that SJS and TEN are a spectrum of the same disease where SJS manifests as less than 10% body surface area skin detachment, while TEN is characterized as greater than 30% skin detachment.[2] Cases involving 10–20% are characterized as SJS/TEN overlap.[2] While SJS/TEN are characterized by cutaneous erythema, blister formation, and hemorrhagic eruptions to mucous membranes as in stomatitis or conjunctivitis, biopsies of lesions demonstrate full-thickness necrosis in EMM but may only show partial necrosis in SJS/TEN. An estimated 1 in every 1000 hospitalized patients has a serious cutaneous drug reaction.[3] The estimated incidence of SJS and TEN is 16 cases/million person-years and 0.4–1.2 cases/million person-years, respectively.[4] Most cases of TEN are drug-induced, with less than 5% of patients reporting no drug use prior to developing TEN.[5] Case reports and studies have implicated over 220 medications as potential causes of SJS/TEN.[6] Common causes of SJS/TEN among antimicrobials include trimethoprim–sulfamethoxazole, aminopenicillins, quinolones, and cephalosporins. The estimated incidence did not exceed 5 cases/per million users for any of these medications.[4]

## Case

An 80-year-old male with a documented unknown allergy to cephalosporins, residing at a long-term acute care hospital,

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was suspected of having a urinary tract infection (UTI) based on a progressive fever and dysuria. A clean catch urine specimen was collected 5 days prior to hospital admission (PTHA) during a scheduled ambulatory dialysis session, and the patient was empirically started on cephalexin. Urine analysis was positive for large leukocyte esterase and bacteria, and culture subsequently grew *Escherichia coli*, 10,000–50,000 cfu/mL demonstrating resistance to ampicillin, levofloxacin, trimethoprim, and sulfamethoxazole; intermediate sensitivity to ampicillin/sulbactam; and sensitivity to cefazolin, gentamicin, and nitrofurantoin. The patient was prescribed cephalexin 500 mg three times daily, and 2 days PTHA, he started to develop an extensive erythematous rash which developed into sloughing of the skin. There was continued progression of this severe reaction, and on day 4 after first receiving cephalexin, the drug was discontinued and the patient was transferred to a local burn intensive care unit (BICU). The patient's past medical history was notable for chronic obstructive pulmonary disease, type 2 diabetes mellitus, coronary artery disease, hypertension, hypothyroidism, depression, and end-stage renal disease (ESRD) requiring hemodialysis. The patient had a history of multiple myocardial infarctions with subsequent ischemic cardiomyopathy, and atrial fibrillation. The patient's home medications included hydrocodone/acetaminophen, levothyroxine, escitalopram, carvedilol, guaifenesin, docusate, calcitriol, albuterol, and amiodarone. Within 24 h of admission, the patient developed pulmonary infiltrates with respiratory failure for which he was intubated.

Upon admission to the BICU, the patient reported difficulty swallowing and an endotracheal tube was placed. The patient was diagnosed with toxic epidermal necrolysis syndrome (TENS) estimated to cover approximately 56% of the total body surface area, involving his entire back, lower chest, abdomen, bilateral upper extremities, and bilateral thighs. Remarkable vital signs and lab results were the following: blood pressure 81/45 mm Hg, respiratory rate 12 breaths/min, temperature 36.8 °C over the temporal artery, with a white blood cell (WBC) count of $1.5 \times 10^3/mm^3$ with 73% neutrophils, platelet (PLT) count of 77,000/μL, serum creatinine (SCr) of 2.12 mg/dL, and venous serum lactate 3.1 mmol/L. His oxygen ($O_2$) saturation was 99% on 6 L $O_2$ via nasal cannula, which was quickly advanced to 15 L via a non-rebreather mask. Pain was assessed at 9 within a 10-point pain scale, with 10 points depicted as the worst imaginable pain.

Two peripheral blood cultures were obtained, as were skin surveillance cultures of nares, axilla, and groin, and a urine culture from a newly placed indwelling Foley catheter. Shortly after, a chest radiograph revealed right pleural effusion with right lower and left basilar opacities. With the patient exhibiting marked respiratory distress, he was then intubated. He was placed on norepinephrine and vasopressin drips for pressure support, as well as continuous infusion of albumin 25%. Lactated Ringer's was given at 300 mL/h, titrated to the patient's urine output. He was administered tetanus–diphtheria toxoids vaccine intramuscularly. Given his reaction was strongly suspected due to a beta-lactam antimicrobial, the 80-kg patient was given single intravenous (IV) dose of gentamicin 120 mg and fluconazole 100 mg.

The following morning (hospital day 2), the patient's WBC was $5.4 \times 10^3/mm^3$, SCr 1.98 mg/dL, and venous serum lactate 1.8 mmol/L. A random serum gentamicin level (22.5 h post-dose) was 2.4 mg/dL, and the patient was redosed with 120 mg of gentamicin 3 h later. Supportive continuous renal replacement therapy was ordered, and fluconazole continued at 200 mg IV every 24 h as early results of his urine culture showed >100,000 cfu/mL *Candida* species. The Gram's stain of the tracheal aspirate performed late the evening before showed heavy growth of pleomorphic Gram-negative rods and diphtheroid-like Gram-positive rods. On day 4 of hospitalization, the patient developed wide complex tachycardia and amiodarone was restarted. Gentamicin was held as a random serum level returned at 2.2 mg/dL. Physical examination performed on hospital day 5 revealed sloughing of skin over his back, chest, upper extremities, abdomen, bilateral thighs, and buttocks. Culture and sensitivity results of the tracheal aspirate grew *Pseudomonas aeruginosa*, sensitive to all anti-pseudomonal beta-lactams as well as gentamicin, tobramycin, amikacin, and colistin, but resistant to doripenem and quinolones. Another 120 mg dose of gentamicin was administered as a random gentamicin level returned under 2 mg/dL, but the patient continued to decline and expired on hospital day 6. The cause of death listed was cardiac arrest, a consequence of multisystem organ failure due to TENS. An autopsy of the chest and abdomen was performed with full-body external examination. The autopsy reported TEN involving 80% of body surface area, as well as necrotizing bronchopneumonia, a very poor prognostic indication for survival.[7,8] A Severity of Illness Score for TEN (SCORTEN) calculated by pathology at the time of autopsy estimated a predicted mortality of 62%.[9]

## Discussion

The most common reactions to cephalosporins are skin reactions such as maculopapular exanthema and urticaria that appear in 1–3% of patients.[10] A case–control study of 245 patients with SJS/TEN contained 14 cases which were associated with cephalosporins.[4] The multivariate relative risk for cephalosporins was 14 (95% confidence interval (CI): 3.2–59) compared to 172 (95% CI: 75–396) for trimethoprim–sulfamethoxazole, which had the highest relative risk for SJS and TEN.[4] The association of cephalosporins with TEN is relatively infrequent, given the high volume of prescriptions for these agents and clear causality is even rarer. There are scattered case reports of second- and third-generation cephalosporins including cefoxitin, cefuroxime, ceftazidime, and ceftriaxone temporally associated with the development of TEN.[11–15] The first-generation cephalosporin, cephalexin, has

been described in several case reports.[16–20] McArthur and Dyment[16] reported the first potential reported case of SJS/TEN associated with cephalexin in a 9-month-old male. That patient received a 10-day course of ampicillin and presented with fever, an upper respiratory tract infection, and widespread maculopapular eruptions. This rash resolved within 24 h. After 10 days, he was diagnosed with otitis media, treated with cephalexin, and a rash appeared 3 days later. The cephalexin was discontinued after an additional 2 days of treatment, and the baby presented the following day (day 6 after starting cephalexin) with a generalized, erythematous maculopapular eruption. This progressed to confluent erythematous squamous macules over the face, trunk, and limbs, as well as ulcers on the palate and lips. He was diagnosed with SJS. The patient was treated with oral fluids and prednisone and discharged after 15 days of hospitalization. Although cephalexin was the likely cause, the patient did also receive ampicillin prior to development of SJS.[16]

Two additional cases were reported in 1987.[17,18] Harnar et al.[17] describe a 74-year-old female who developed TEN after a 12-h course of cephalexin and thioridazine for dysuria and nervousness. The epidermal slough progressed to cover 30% of her total body surface area. The patient was treated early with IV fluids, urgent debridement, and IV antibiotics. Despite the aggressive care, the patient developed multisystem organ failure and expired on the 37th day. Again, it was not known whether the cephalexin or thioridazine caused the TEN.

Hogan and Rooney[18] report a 53-year-old woman who developed diffuse, confluent erythema and bullae on her legs and body 2 days after taking cephalexin. She had superficial blisters involving most of her legs as well as erythema on the back and arms. The patient only received conservative treatment and fully recovered. This was the first case of SJS/TEN for which cephalexin was the sole suspect.

Dave et al.[19] report a case in the United Kingdom involving a 61-year-old female who received cephalexin for an upper respiratory tract infection. After 2 days, she developed a pruritic, erythematous rash over her trunk and limbs, at which time the cephalexin was discontinued. Over the next 3 days, she developed ulceration involving 75% of her body accompanied by multiorgan failure. Following 5 weeks of intensive care, she developed an irreversible bronchospasm of unknown etiology and expired.

Murray and Camp[20] describe a 32-year-old female with systemic lupus erythematosus who presented with a diffuse pruritic rash and oral ulcers 2 weeks following treatment with cephalexin. The rash started on day 6 of therapy, and the cephalexin was discontinued the following day. Twelve days after starting the cephalexin, the patient was admitted to the hospital with increased pruritus, worsening oral ulcers, and increased pain in her lower extremities. Examination on admission showed scarring alopecia and erythema over 75% of her scalp, diffuse violet macular rash with erythema, multiple bullous lesions on her neck and abdomen anteriorly, and several macules. She was treated with fluids, parenteral nutrition, and steroids. On day 10, she resumed a soft diet and was discharged.

Brand and Rohr[21] describe 67-year-old male who developed TEN 14 days following a cephalexin exposure for which he was hospitalized 90 days. Previous case reports of cephalexin-associated SJS/TEN are summarized in Table 1.

Large database surveillance studies have identified 5 other cases of SJS/TEN attributed to cephalexin, but details are not given about these cases and therefore are not included in Table 1.[22–24] Jick and Derby[22] identified 1 case of TEN in a patient who took cephalexin. Platt et al.[23] and Ding et al.[24] each identified 2 cases of SJS/TEN involving cephalexin.

Unfortunately, in the case we presented, the patient's past allergic reaction to cephalosporin(s) was unknown. The prescribed dose of cephalexin 500 mg three times daily was not appropriate for someone in ESRD. A dose of 250–500 mg twice daily would have been more appropriate and would have resulted in less drug accumulation. The patient was not prescribed any other new medications within 1 month of him developing TENS. Given the patient's reaction to beta-lactam agents, there were few antibiotic classes that demonstrated activity against the *E. coli* isolate. Aztreonam could have been an option, but gentamicin was chosen given the sensitivity pattern and the ability to monitor the medication in the acute phase. The timeframe of 2–3 days for the development of a rash, which then progressed to sloughing of the skin was consistent with previous TENS cases. A conservative estimate of the Naranjo algorithm was scored 6 points for this case, falling in the category of "probable adverse drug reaction." This patient case was identified by a quality control committee which recognized this severe drug reaction. All documentation connecting this case to the patient was stored on a personal password protected computer, in a locked office. Patient confidentiality has been maintained by destroying all patient identifiers linked to this case.

## *Clinical presentation*

Presentation of symptoms of drug-induced SJS/TEN typically occurs 1 to 3 weeks after the start of drug therapy, but occurs sooner after rechallenge.[5] No clinical test exists for accurately identifying the cause; therefore, obtaining an accurate history is essential for diagnosing SJS/TEN. A differential diagnosis should be made from EMM, impetigo, lupus erythematosus, linear IgA dermatosis, staphylococcal scalded skin syndrome, pemphigus vulgaris, bullous pemphigoid, graft versus host disease, and thermal or chemical burns.[6] The prodromal phase of SJS and TEN may last from 1 day to 2 weeks and usually manifests as influenza-like symptoms including high fever, cough, myalgias, arthralgias, and malaise.[25] Mucosal involvement may manifest as conjunctivitis or various oral lesions. This is followed by flat, irregular, atypical target lesions or diffuse purpuric macules frequently with necrotic centers (more common in

**Table 1.** Summary of SJS/TEN cases associated with cephalexin.

| Case | Demographics | Medical conditions | Cephalexin dose | Signs and symptoms | Hospital course | Syndrome/% of skin involvement | Outcomes |
|---|---|---|---|---|---|---|---|
| McArthur and Dyment16 | 9-month-old male | Fever and respiratory infection | Not reported | A rash developed 4 days after completing 10-day ampicillin therapy and lasted 24 h. After 10 days, patient was prescribed cephalexin for otitis media and tonsillitis. A similar rash appeared 3 days later. Drug discontinued after 5 days. Ulcers on palate and lip appeared 5 days later | Rash on face, trunk, and limbs covered with macules. SJS resolved | SJS/not reported | Recovered, discharged after 15 days |
| Harnar et al.17 | 74-year-old female | Not reported | Not reported | Prescribed a 12-h course of cephalexin and thioridazine for dysuria and nervousness. Developed epidermal slough soon after | Developed severe wound sepsis despite fluids, urgent debridement, and IV antibiotics. Patient expired on 37th day | TENS/30% | Expired (sepsis) |
| Hogan and Rooney18 | 53-year-old female | Not reported | Not reported | Prescribed cephalexin for erythema and swelling of the left knee. Second day of treatment developed diffuse, confluent erythema that was pruritic | Bullae developed on the legs and body. Superficial blisters noted on most of the legs. Responded to conservative management | TENS/not reported | Recovered, length of stay not reported |
| Dave et al.19 | 61-year-old female | Not reported | Not reported | Prescribed cephalexin for an upper respiratory tract infection. Developed erythematous rash 2 days later. | Admitted 5 days after starting cephalexin with ulceration | TENS/75% | Expired (sepsis) |
| Murray and Camp20 | 32-year-old African American female | Systemic lupus erythematosus | Not reported | Prescribed cephalexin for possible bronchitis. Developed rash on day 6 of therapy. Stopped on day 7 in emergency room. Admitted 12 days after start of therapy for increased pruritus and oral ulcers. | Treated with fluids, parenteral nutrition, steroid, and steroids. | SJS/not reported | Recovered, discharged after 10 days |
| Brand and Rohr21 | 67-year-old male | Not reported | Not reported | No details given | No details given | TENS/not reported | Not reported |

SJS: Stevens–Johnson syndrome; TENS: toxic epidermal necrolysis syndrome.

TENS).[26] Skin lesions often begin symmetrically on the trunk, upper extremities, face, and spread to the neck, with rare involvement of the legs arms.[6] With ensuing damage and death of keratinocytes and the mucosal epithelium, the epidermis detaches from the skin, producing blisters. In TEN, this appears sheet-like, and patients frequently have a positive Nikolsky sign.[26] The most common cause of death is septicemia, with *Staphylococcus aureus* or *Pseudomonas aeruginosa* being the most common culprits.[27]

### *Immunopathology*

In SJS/TEN, the offending drug induces keratinocyte and mucosal epithelial cell death.[6] This process is thought to be mediated by T lymphocytes with involvement of monocytes and macrophages, although the literature is replete with several competing models.[6,28] During SJS/TEN, monocytes–macrophages, keratinocytes, and granzyme B proteins release Fas–FasL (ligand) and tumor necrosis factor (TNF)-alpha which act as signals for apoptosis.[6] This leads to an increase in death of keratinocytes, which can eventually manifest as SJS or TEN presentation.[29] Among patients with SJS or TEN compared to healthy adult comparators, Murata et al.[29] have demonstrated the FasL serum levels of patients with SJS or TEN are significantly increased before the development of either skin detachment or mucosal lesions.

### *Treatment*

There is no uniform treatment strategy for treating SJS/TEN. Treatment of SJS/TEN generally includes immediate withdrawal of the offending agent and referral to a burn center or intensive care unit.[26] First-line therapy involves maintaining fluid status with crystalloids, balancing electrolytes, thermoregulation, blood glucose control, and wound management.[6,26] Patients should be started on total parenteral nutrition if unable to fulfill nutrition requirement by mouth.[6] Since these patients are critically ill, patients should be given analgesic medications, deep vein thrombosis prophylaxis, stress ulcer prophylaxis, and prevention of infection and pressure ulcers is essential.[6]

Wound care is an important aspect of all patients with SJS/TEN. Areas of debridement should be covered with clean bandages and replaced regularly. The dressing should be water vapor-permeable, non-toxic, non-adherent, durable, comfortable, and easy to apply.[30,31] Silver sulfadiazine can be an effective agent as long as the patient is not sulfa-sensitive; however, not everyone agrees on its use due to potential systemic sensitization and leukopenia.[6] Skin grafts and biological materials are an option in some patients.

Several adjuvant medications are available for the treatment of SJS/TEN. Corticosteroids became a popular treatment due to the immunogenic response associated with SJS/TEN but have remained controversial due to conflicting evidence.[6,27] Their routine use is currently not recommended due to the suppression of the immune system and increased risk of infections.[6] Other potential therapies include IV immunoglobulin, cyclosporine, cyclophosphamide, plasmapheresis, TNF-alpha inhibitors, N-acetylcysteine, and hemodialysis. These therapies are, in general, anecdotal and are lacking robust data or analysis from well-structured clinical trials.

## Summary

This case represents a fatal case of TEN, likely caused by cephalexin. The incidence of SJS/TEN induced by cephalexin is extremely rare, especially given the large volumes of cephalexin prescriptions dispensed and doses taken by patients in the United States. A Department of Health and Human Services memo from the Food and Drug Administration's Office of Surveillance and Epidemiology in 2009 revealed cephalexin accounted for 86% of the first-generation cephalosporin market.[32] While SJS/TEN are rare in cephalosporins, they should be considered as agents that can potentially cause SJS and TEN.

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