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# Oral Cyclosporine Treatment for Four Pediatric Patients With Toxic Epidermal Necrolysis That Showed No Response to High-dose Corticosteroids in Combination With Intravenous Immunoglobulin: A Case Series

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ABSTRACT

*Background:* Immunosuppressive agents like cyclosporine have proven effective in some pediatric cases, although there are limited case reports considering potential risks such as secondary infections.
*Objective:* This study investigated the safety and efficacy of Cyclosporine A in children who did not respond to high-dose corticosteroids combined with intravenous immunoglobulin (IVIG).
*Methods:* We reported four pediatric patients diagnosed with toxic epidermal necrolysis (TEN) received treatment at our institution. All patients were previously healthy children with a median age of 7 years, comprising three boys and one girl (Table 1). Epidermal exfoliation and vesicular lesions ranged from 32.5% to 54.5% of the body surface area (BSA). Despite the administration of treatment comprising high-dose corticosteroids and intravenous immunoglobulin (IVIG), new cutaneous herpes continually emerged. This prompted a transition to cyclosporine treatment (3–5 mg/kg/d) administered in 1–2 oral doses.
*Results:* Lesions stopped progressing, and bullous lesions started epithelialization after 13–27 days of hospitalization. Cases 1 and 2 faced secondary bacterial and fungal infections, respectively, and their temperatures stabilized after administration of antibiotics. Cases 3 and 4 experienced fever again when the dosage of corticosteroids was tapered off, with no discernible evidence of infection. The patients' temperatures normalized upon the continuation of cyclosporine therapy. Among the patients, three presented asymptomatic elevated serum amylase, one of which met the diagnostic criteria for acute pancreatitis. Two children showed mildly raised aminotransferases, with one experiencing mild coronary artery dilation, two contracted onychomadesis, and three developed corneal ulceration/keratitis and atretoblepharia, which eventually resolved after vigorous ophthalmologic treatment. None of the children had any permanent sequelae after being discharged from the hospital for six months.
*Conclusions:* Cyclosporine A is generally safe and effective for children who fail to respond to high-dose corticosteroids in combination with IVIG.



## Introduction

Toxic epidermal necrolysis (TEN) is a severe form of the condition where epidermolysis bullosa affects over 30% of body surface area (BSA) with high fatality rate ranges from 14.8% to 46%.[1–3] The treatment of TEN lacks high-level evidence-based medical support. Intravenous corticosteroids and intravenous immunoglobulin (IVIG) are commonly prescribed for pediatric patients. Immunosuppressive agents like cyclosporine have proven effective in some pediatric cases, although there are limited case reports considering potential risks such as secondary infections.[4,5] The optimal dosing of cyclosporine for TEN has not been standardized, literature suggests that 3 to 5 mg/kg body weight proves successful.[6,7] Herein we report four child cases with TEN, initially treated with IVIG and high-dose corticosteroids. This regime wasn't optimally effective, the addition of oral cyclosporine therapy became viable, as witnessed in postdischarge follow-ups. The severity of skin and

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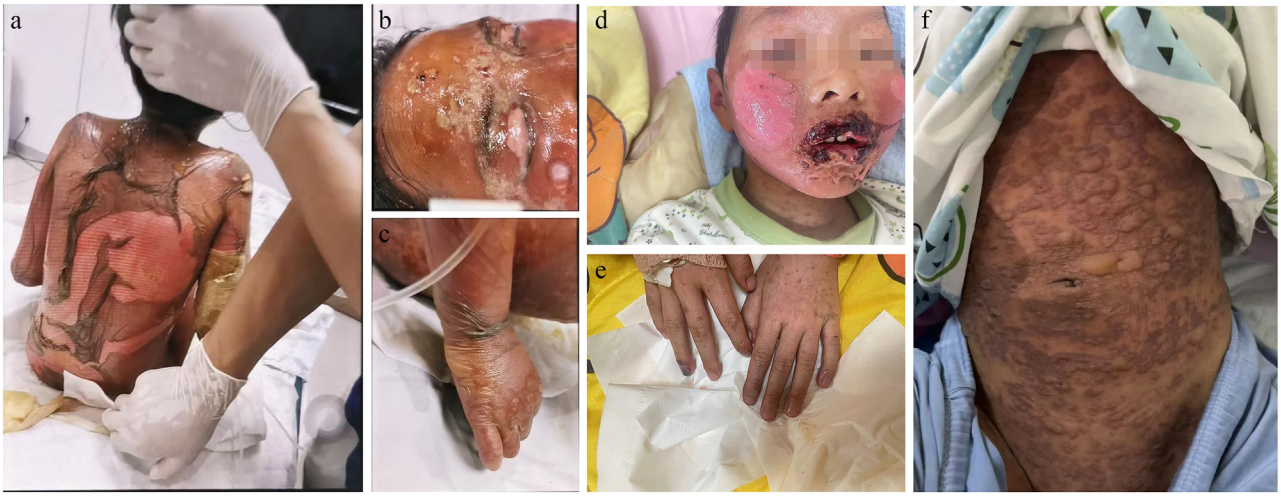


**Figure.** Toxic epidermal necrolysis. (A–F) Prior to the oral administration of cyclosporine, exfoliation, and exudation of the epidermis of the eyes, trunk, and hands in case 1 were observed, combined with a Gram-positive coccobacillus infection of the skin (A–C). The lesions of mucous membranes of the lips, as well as the facial skin, were presented in case 2 (D). In case 3, nail lesions was observed before onychomadesis (E). In case 4, blisters formed on an erythematous base of the epidermis in the trunk (F).

mucosal damage observed in this case surpasses that of previously reported instances. The utilization of cyclosporine therapy following the administration of IVIG and high-dose corticosteroid shock therapy, particularly in the presence of complex infectious factors, provides valuable insights.

## Case Description

**Case 1** (No.1 in TABLE 1): A 7-year-old girl who 12 days prior, exhibited symptoms of fever, conjunctival congestion, and rash (Figure A–C). Initial treatment administered at another hospital included intravenous dexamethasone (0.8 mg/kg/day) for 11 days, IVIG 1 g/kg for a cumulative of 2 days, 10-day acyclovir, 5-day azithromycin, 10-day meropenem, 12-day linezolid, 2-day fluconazole, along with intravenous rehydration fluids and albumin. Despite this multifaceted treatment leading to temporary normalization of her temperature, her skin and eye lesions persisted in existing and progressing. At the point of admission to our institution, the skin across her face, neck, trunk, limbs, and perineum was extensively detached, displaying some epidermal exfoliation and fresh trauma. Epidermal exfoliation was charted at up to 54.5% of BSA, and the lip and oral mucous membranes were seen to have vesiculated and split, exhibiting hardened black blood crusts. These alterations caused restriction in mouth opening and vision obstruction. Both eyes exhibited impaired opening, and the bulbar conjunctiva was congested and exuding. Ophthalmologic consultation revealed the presence of atretoblepharia and corneal ulcers. The patient exhibited normal physiological status with appropriate growth and development stages, no medication history for the 2-month period before disease onset.

Routine tests showed normal blood count, CRP at 12.87 mg/L, biochemical ALB at 28.5 g/L, and sodium at 129 mmol/L. Her liver and kidney functions and cardiac enzymes were all standard. The pathogenic test results indicated presence of herpes simplex virus (HSV), reactivated Epstein–Barr virus (EBV), and Mycoplasma pneumoniae (MP). On disease, day 2, cytokine readings showed IFN-$\gamma$ >1000 pg/mL, TNF-$\alpha$ 30.21 pg/mL, IL-6 56.37 pg/mL, IL-8 183.9 pg/mL, and IL-10 153.12 pg/mL. Lymphocyte subpopulations included: CD3+CD4+/CD3+CD8+ 0.92 (normal values 1–2), CD19+ cells at 26.95% (6–18), and CD16+CD56+ cells at 5.55% (8–26). By disease day 10, cytokines IFN-$\gamma$ was reported as normal, TNF-$\alpha$ at 8.73 pg/mL, IL-6 at 90.57 pg/mL, and IL-8 at 76.72 pg/mL, with normal IL-10.

She was admitted to the pediatric intensive care unit (PICU) immediately and cyclosporine 3 mg/kg/day was initiated. However, a week later, high fever recurred indicating a complication of the Gram-positive coccus infection. Applying linezolid for 1 week achieved temperature normalization. An elevated serum amylase (1024 U/L) appeared on disease day 14, despite no symptoms of abdominal pain and vomiting, no pressure pain on abdominal examination, and abdominal ultrasonography not revealing any morphological abnormality of the pancreas. Reepithelization was achieved on the 27th day revealing detached nails and subsequently, on the 33rd day, the patient was transferred from the PICU to the general ward, finally getting discharged from the hospital on the 39th day. No sequelae were observed after 6-month follow-up.

**Case 2** (No.2 in TABLE 1): A 4-year-old boy who presented with high fever and cough followed by a rash that began as maculopapular eruptions on the face, which progressively spread and merged, forming blisters across the body (Figure D). Accompanying symptoms included conjunctival congestion, exudation, cracked lips, and oral cavity vesiculitis with ulceration. Blisters also formed in the perianal region, causing epidermal exfoliation of up to 49% of BSA. With consultation from the Department of Infectious Disease, differential diagnoses excluded hand-foot-mouth disease.

The blood panel showed Neutrophils at 77.7%, CRP at 9.17 mg/L, IL-6 at 274.47 pg/mL, PCT at 7.41 ng/mL, ALT at 41.97 U/L, and AST at 76.85 U/L. Despite persistent high fever, the patient showed increased respiration, maintaining an oxygen saturation of 93% without supplemental oxygen. Emergency CT scans revealed bilateral pneumonia, prompting admission to the PICU, where he was diagnosed with TEN. The patient was administrated methylprednisolone 500 mg IV drip (25 mg/kg) for 5 days, followed by a reduced regimen of 40 mg Q12H, which was transitioned to oral administration and tapered off. Concurrently, IVIG of 1 g/kg IV drip was administered for 2 days alongside meropenem for infection control. Body temperature normalized by day 3 of this treatment, but temperature fluctuations returned upon reduced steroid dosage. New skin herpes outbursts emerged, leading to prescription of cyclosporine at 3.5 mg/kg/day. Day 13 saw cessation of skin lesions as cyclosporine dosage was lowered. The patient reported abdominal pain and vomiting at D9, with serum and urine amylase recorded at 243 and 893 U/L respectively, which normalized following omeprazole treatment. On the 10th day of hospitaliza-

**Table 1**
Four pediatric cases of TEN treated with oral cyclosporine.

| *N* | Age (y) | Sex | Culprit drug | BSA (%) | Onset days before admission | Days of initiation of cyclosporine | Dose of cyclosporine (mg/kg/d) | Days of administration of cyclosporine | Other treatments | Days of re-epithelialization | Inpatient days | PICU days | Concomitant pathogens | Cytokines (pg/mL) | | | ALT (U/L) | Complications |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 7 | F | None | 54.5 | 12 | 13 | 3.0 | 30 | Dexamethasone (0.8 mg/kg/day) + IVIG | HD27 | 39 | 33 | HSV/EBV/MP | IL-6<br>IL-8<br>IL-10<br>TNF-$\alpha$<br>IFN-$\gamma$ | D2<br>56.37<br>183.9<br>153.12<br>30.21<br>>1000 | D9<br>90.57<br>76.28<br>Normal<br>8.73<br>Normal | Normal | *,‖,¶ |
| 2 | 4 | M | None | 49 | 3 | 9 | 3.5 | 10 | Methylprednisolone (25 mg/kg) + IVIG | HD13 | 33 | 24 | None | IL-6 | 274.47 | | 41.97 | †,‡,# |
| 3 | 7 | M | Azithromycin | 50 | 7 | 9 | 4.0 | 12 | Methylprednisolone 20 mg/kg + IVIG | HD13 | 17 | 15 | *Bordetella pertussis*, *Streptococcus pneumoniae*, *Haemophilus influenzae* | IL-6 | 117.95 | | 120.00 | *,†,§,‖ |
| 4 | 7 | M | Acetaminophen | 32.5 | 4 | 10 | 5.0 | 21 | Methylprednisolone at 6–10 mg/kg + IVIG | HD13 | 21 | 12 | HSV/MP | IL-6 | 46.06 | 15.24 | Normal | * |

BSA = body surface area; HD = hospital day; IVIG = intravenous immunoglobulin.
* Corneal ulceration/keratitis and atretoblepharia.
† Mildly raised aminotransferases.
‡ Mild coronary artery dilation.
§ Pancreatitis.
‖ Onychomadesis.
¶ Bacterial infection.
# Fungal infection.

tion, the child experienced a high fever recurrence, and Candida tropicalis was detected in the sputum. The fever resolved following the administration of fluconazole to treat the infection. Initial cardiac ultrasound showed left coronary artery at 3.0 mm and the right at 2.1 mm, but a recheck at D21 saw an increase to 3.3 mm for the left and 2.2 mm for the right. The patient was given clopidogrel orally and was transferred to the general ward on D24 in stabilized condition. He was discharged from the hospital on D33. His coronary arteries became normal 2 months after discharge, and no sequelae were noted from follow-up to 6 months after discharge.

**Case 3** (No.3 in TABLE 1): A 7-year-old male patient presented with a worsening cough that began 7 days prior (Figure E). Despite 3 days of oral Azithromycin treatment, the cough worsened. Two days prior, high fever surfaced, followed by a skin rash that began on the upper limbs and eventually appeared on the face, neck, torso, and other limbs. The rash presented with numerous blisters on the surface that led to epidermal peeling and ulceration. Additional symptoms included conjunctival congestion, exudation, difficulty in opening the eyes, and red, swollen lips with ulceration. Numerous vesicles were also observed on the mucous membrane in the oral cavity.

Laboratory tests suggest Neutrophilia (84.7%), elevated levels of CRP (15.89 mg/L), PCT (0.503 ng/mL), D-dimer (6.41 mg/L), ALT (120 U/L), AST (132.8 U/L), Interleukin-6 (IL-6; 117.95 pg/mL) and amylase (1589 U/L). Hyponatremia was also observed (131 mmol/L). Abdominal ultrasound revealed pancreatic body thickening. Respiratory pathogen targeted sequencing revealed the presence of *Bordetella pertussis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, with a positive throat swab for pertussis nucleic acid. The patient was treated with oral erythromycin for 7 days, IVIG 400 mg/kg/day for 5 days, and methylprednisolone 20 mg/kg/day for 5 days, followed by a reduction to 40 mg/d and gradual tapering off. Fever resolved on the 3rd day of the treatment but new blisters appeared on the 6th day. A 4 mg/kg/day oral dosage cyclosporine was given on 6th day of hospitalization for re-epithelialization. Fever reappeared 5 days after hormone tapering. On the 15th day of hospitalization, the patient was transferred from the PICU to the general ward and discharged from the hospital on the 17th day. No sequelae were observed after 6-month follow-up.

**Case 4** (No.4 in TABLE 1): The patient is a 7-year-old boy. Four days prior, he presented with a fever reaching a peak of 38.9°C, managed initially with oral acetaminophen. Two days later, he developed a rash that initiated on his face and progressively spread across his entire body (Figure F). A day following the onset of the rash, it coalesced, leading to the formation of large blisters all over the body. Accompanying effects included an exfoliating epidermis, eyelid closure, oozing, and blistering lips with blood crust, with the lesion-covered area accounting for 32.5% of BSA.

Laboratory tests revealed IL-6 to be 46.06 pg/mL, an MP total antibody ratio of 1:80, and HSV-IgM positive. The treatment regimen included IVIG with a dosage of 1 g/kg/day for 2 days, followed by Cefoperazone, Acyclovir, and Methylprednisolone at 6 mg/kg/day for 3 days, augmented to 10 mg/kg/day for another 3 days. While there was reduction in fever mildly, the skin condition continued to progress. Consequently, the patient was transferred to the PICU where he received oral cyclosporine at 5 mg/kg/day. The skin started to re-epithelize on 13rd day of hospitalization, but the fever recurred on 9th day. Laboratory tests confirmed absence of pathogenic in the blood culture and metagenomic next-generation sequencing of throat swab. Subsequent to fever normalization around 5 days, the patient was transferred back to the general ward. Then he was discharged from the hospital on the 22th day. No permanent sequelae were observed after a 6-month follow-up.

## Discussion

TEN is primarily a specific T cell-mediated response with activation of specific cytotoxic CD8+T cells and subsequent release of cytotoxic proteins leading to epidermal necrolysis and loosening of the epidermis, and a variety of cytokines/chemokines are also involved in the pathogenesis.[8–11] The mechanism of action of cyclosporine in TEN is to inhibit T-cell activation, thereby preventing cytotoxic T-cells and natural killer cells from producing and releasing cytokines, which are critical to the pathogenesis and dissemination of TEN.[12,13] Twenty-four studies with 979 patients were included in a meta-analysis in 2021, and direct pairwise comparisons showed that the mortality rate was lower in the cyclosporine group than the IVIG group (OR 0.08, 95% CI 0.01–0.54). Rank ordering showed cyclosporine to be the most effective therapy, followed by corticosteroids + IVIG, and etanercept.[14] The four children in this report tested significantly elevated for a variety of cytokines, which may account for the ineffectiveness of high-dose corticosteroids and IVIG. In four children, the median time to achieve re-epithelialization was 13 days, with case 1 experiencing a maximum of 27 days. Initially, this patient exhibited particularly high IFN-$\gamma$ levels and had the most severe involvement of skin and mucous membranes, along with the latest initiation of cyclosporine treatment, which illustrated the importance of early application of cyclosporine.

Patients receiving immunosuppressive therapy, including cyclosporine and cyclosporine-containing dosing regimens, are at increased risk for infections (viral, bacterial, fungal, parasitic), both systemic and localized, and pre-existing infections may be exacerbated. Serious or fatal events have been reported.[10,15,16] All four children were previously healthy with no underlying diseases. Upon admission, their lymphocyte subsets and immunoglobulin levels did not indicate any form of immunodeficiency. The presence of HSV and EBV infections in case 1, *S. pneumoniae*, pertussis, and *H. influenzae* infections in case 3, HSV and MP infections in case 4, and the initial failure to detect any pathogen in case 2, and the detection of Candida tropicalis infection in the course of the treatment for fever, suggests that systemic immunosuppressant administration does carry a risk of secondary infections, but is not fatal. The use of IVIG alone does not seem to be supported by sufficient evidence for controlling the progression of TEN, but its immunosuppressive effect may be effective in preventing infections that may occur during TEN treatment.[17,18] In addition nutritional support, appropriate management of skin wounds, care of the mucous membranes of the eye, mouth and external genitalia and protection of the gastrointestinal mucosa are also important therapeutic aspects.

The limitations of this study include its retrospective observational design, the lack of standardization in treatment regimens and dosages, and inconsistency in the testing of cytokines. Additionally, cyclosporine was not administered from the beginning of treatment but was introduced after other therapies, making it difficult to attribute the observed effects solely to cyclosporine. Nevertheless, the noticeable improvement in re-epithelialization suggests a potentially positive effect of cyclosporine, and future studies are needed to include controls for validation.

## Conclusions

In the four cases reported in this study, cyclosporine proved effective for children with TEN who did not respond to high-dose corticosteroids and IVIG. Furthermore, early administration of cyclosporine may expedite re-epithelialization. The secondary infections that follow are nonfatal. Given the limited number of pediatric patients in this study, additional research, including

randomized clinical trials, is needed to evaluate the efficacy and safety of cyclosporine in the pediatric population.

## Patient Consent

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

## CRediT authorship contribution statement

**Peijing Li:** Writing – original draft. **Qin Yao:** Methodology, Data curation. **Yuanyuan Wang:** Methodology, Data curation. **Xipeng Xu:** Writing – review & editing, Supervision.

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