

# Combination of cyclosporine A and methylprednisolone to treat pediatric Stevens-Johnson syndrome/toxic epidermal necrolysis overlap syndrome

Shinta Trilaksmi Dewi,<sup>1</sup> Laily Noor Qomariah,<sup>2</sup> Widya Khairunisa Sarkowi,<sup>3</sup> Monika Puspitasari,<sup>1</sup> Miya Khalidah,<sup>1</sup> Marcella Anggata,<sup>1</sup> Dwinanda Almira Rizkiani,<sup>1</sup> Kristiana Etnawati,<sup>1</sup> Sri Awalia Febriana<sup>1</sup>

<sup>1</sup>Department of Dermatology and Venereology, Faculty of Medicine, Public Health and Nursing, Gadjah Mada University, Yogyakarta;

<sup>2</sup>Wates Government District Hospital, Kulon Progo, Yogyakarta; <sup>3</sup>Faculty of Medicine, IPB University, Bogor, West Java, Indonesia

## Abstract

The treatment of epidermal necrolysis in pediatric patients remains a major challenge. Cyclosporine A has emerged as a promising therapy for epidermal necrolysis in adults; however, its efficacy in children is unclear. We present the case of a boy with

Stevens-Johnson syndrome/toxic epidermal necrolysis overlap syndrome who was initially resistant to methylprednisolone monotherapy but improved after receiving the combination of cyclosporine A and methylprednisolone. Published reports on the use of cyclosporine A for pediatric epidermal necrolysis are also briefly reviewed.

Correspondence: Shinta Trilaksmi Dewi, Department of Dermatology and Venereology, Faculty of Medicine, Public Health and Nursing, Gadjah Mada University, Jl. Farmako Sekip Utara, Depok, Sleman, Yogyakarta 55281, Indonesia.  
Tel.: +62.274-560700.

E-mail: shinta.trilaksmi.d@ugm.ac.id

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## Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening skin reactions caused by drugs or infections and characterized by extensive blisters and necrosis affecting the mucocutaneous surface. Both conditions involve epidermal necrolysis with different degrees of severity, with SJS affecting <10% body surface area (BSA) and TEN attacking >30% BSA. SJS/TEN overlap syndrome occurs when 10-30% BSA is involved.<sup>1</sup>

SJS and TEN in children are extremely rare with only 5.3 and 0.4 cases per million children, respectively.<sup>2,3</sup> Nevertheless, pediatric SJS/TEN has high rates of complications, sequelae, and recurrences.<sup>4,5</sup> Evidence on effective treatments for pediatric SJS/TEN is lacking, and most guidelines are adopted from adult versions. The efficacy of standard therapies, such as systemic steroids and intravenous immunoglobulins (IVIGs), remains inconsistent. In recent years, evidence demonstrating the benefit of cyclosporine A (CsA) for adult SJS/TEN has accumulated; however, only a few reports indicated the efficacy of CsA for treating SJS/TEN in children. Here, we present a pediatric patient with SJS/TEN overlap syndrome who was successfully treated with a combination of CsA and methylprednisolone.

## Case Report

An 8-year-old boy was referred to our hospital due to painful rashes, conjunctivitis, and lip erosion. Seven days before hospital admission, his parents gave him paracetamol because he was feeling unwell. When he developed a fever and cough three days later, his parents took him to a local midwife, who prescribed paracetamol, chlorpheniramine maleate, and an unidentified antibiotic. The parents admit that they often give him mixed medicines in the form of powder from the midwife whenever their son is sick. One day after taking these medicines, a rash appeared and progressively developed into blisters on the face, neck, trunk, and extremities. Upon initial examination, the patient looked weak and had a temperature of 37.9°C. Dermatological examination revealed dusky erythematous patches with Nikolsky-positive blisters and erosions on the abovementioned areas, involving approximately 10% BSA (Figure 1a). He also experienced bilateral conjunctivitis, stomati-

tis, and crusted erosions on his lips. A diagnosis of SJS suspected due to paracetamol, chlorpheniramine maleate, or an unidentified antibiotic was made. Laboratory tests demonstrated leukopenia ( $2.9 \times 10^3/\text{mL}$ ) with an elevated C-reactive protein (82 mg/L). Serology tests for herpes simplex virus-1 and -2 showed negative results for both Immunoglobulin (Ig) M and IgG, excluding an infection cause. SCORTEN was 0, corresponding to a 3% mortality risk. Suspected drugs were discontinued, and supportive care with methylprednisolone administration at 2 mg/kg/day was initiated. Over the first 6 days of hospitalization, the skin condition

worsened with the formation of new blisters involving 15% BSA. A new diagnosis of SJS/TEN overlap syndrome was made (Figure 1b). CsA at a dose of 2.5 mg/kg/day was added to the treatment. Twenty-four hours following CsA therapy, the formation of new blisters stopped. Complete re-epithelialization was obtained by day 18 of hospitalization or day 12 of CsA therapy, with crusts remaining on the lips (Figure 1c). The methylprednisolone dose was slowly tapered off, and both drugs were discontinued by day 17. The patient was discharged after 22 days of hospitalization (Figure 2).



**Figure 1.** a) On the day of admission, dusky erythematous patches, blisters, and erosions were found, and 10% body surface area (BSA) involvement was noted; b) on day 6 of hospitalization or before the initiation of cyclosporine A (CsA), the skin condition worsened with the formation of new blisters, particularly on the face, and 15% BSA involvement was noted; c) on day 18 of hospitalization or 12 days of CsA therapy, complete re-epithelialization was achieved.

## Discussion

SJS/TEN overlap syndrome in children shows the same clinical presentations as in adults. Following the prodromal symptoms of fever, sore throat, and cough, cutaneous lesions appear as erythematous macules on the trunk and progressively develop into confluent dusky-red patches, flaccid blisters, and large areas of denudation. Erosions of two or more mucosal surfaces are commonly present, with oral mucosa being the most frequently involved, followed by ocular and genital mucosa.<sup>1</sup> Although pediatric SJS/TEN has a low mortality rate,<sup>6</sup> it has various risks, including high recurrence, long-term complications, and sequelae.<sup>4,5</sup>

Many aspects of epidermal necrolysis pathophysiology have not been fully elucidated.

Nevertheless, the widespread damage of keratinocytes is postulated to be the key main event in SJS/TEN. The triggering drugs (or infectious agents) induce type IV hypersensitivity mediated by the cytotoxic mechanisms of CD8<sup>+</sup> T cells and NK cells. The activation of these cells, directly and indirectly, induces the killing of keratinocytes through the release of pro-inflammatory apoptosis-inducing mediators, including granulysin, perforin/granzyme B, tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), interleukin (IL)-15, and fas ligands. Granulysin has recently become the main target of therapy because its serum level is correlated with the severity of SJS/TEN.<sup>7</sup>

Immunosuppressive agents, such as corticosteroids, IVIGs, CsA, or TNF $\alpha$  inhibitors, are often given as an adjunct to the withdrawal of suspected drugs and supportive care as the mainstay of treatment to control disease progression.<sup>1</sup> However, the efficacy of these drugs is variable, and prospective studies are limited due to the rarity of the condition. Corticosteroids are currently the most used drugs for adults and children. Nevertheless, a recent meta-analysis confirmed the insignificant benefit of their use as monotherapy.<sup>8</sup>

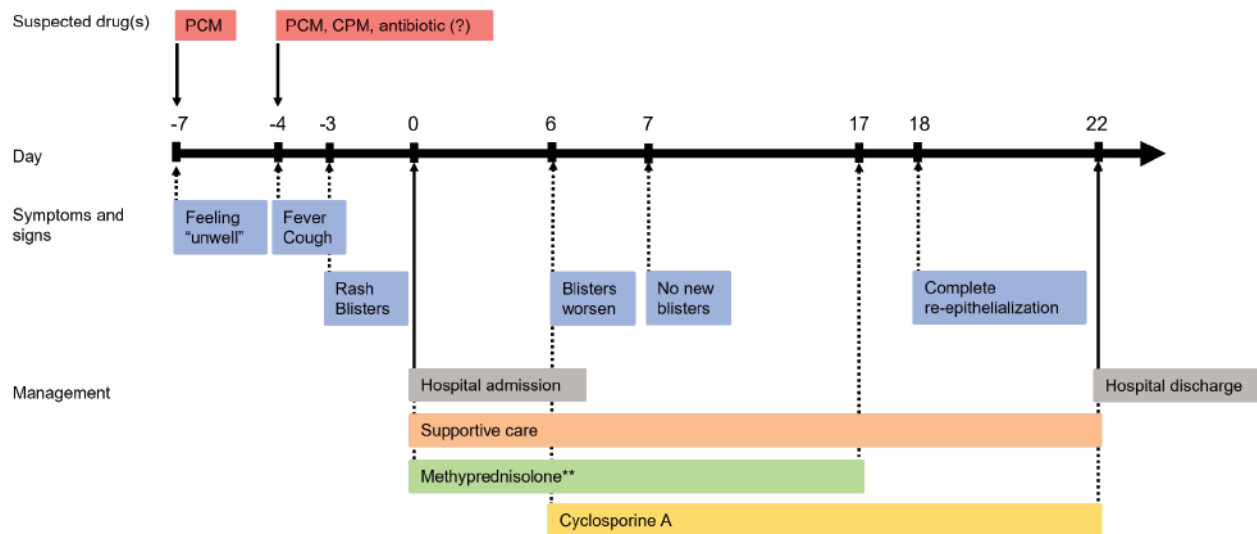
The successful use of CsA for epidermal necrolysis in adults was first reported in 1989.<sup>9</sup> Since then, results on its efficacy in controlling SJS/TEN have been inconsistent.<sup>10</sup> No randomized controlled trials have been conducted, but meta-analyses indicated a survival benefit of CsA compared with supportive care for

SJS/TEN.<sup>1</sup> Further research demonstrated that treatment with the addition of CsA was linked to a higher re-epithelialization rate, shorter duration of hospital stay, and lower risk of systemic infection in adults with SJS/TEN compared with that without CsA.<sup>11</sup>

Evidence on CsA use in pediatric SJS/TEN is limited. Only ten case reports have been published, and all of them described favorable outcomes (Table 1).<sup>12-19</sup> The youngest patient reported was 17 months old, and the oldest was 17 years old.<sup>12,13</sup> Among these 10 patients, 6 (60%) were female and 4 (40%) were male. In terms of BSA involvement, the efficacy of CsA therapy was demonstrated in four cases of pediatric SJS/TEN overlap syndrome<sup>13,14</sup> and six cases of pediatric TEN.<sup>12,15-19</sup> Our case showed the benefit of adding CsA to the treatment for SJS/TEN overlap syndrome in an 8-year-old boy, further supporting its favorable use in pediatric SJS/TEN.

Among the reported cases, CsA was given as monotherapy to four patients and CsA combined with other drugs, including corticosteroids,<sup>13,15,16</sup> IVIG,<sup>18</sup> corticosteroids and IVIG,<sup>17</sup> or corticosteroid and etanercept, was administered to six patients.<sup>12</sup> The dose of CsA for monotherapy was 3-4 mg/kg/day, with variable dose tapering depending on the patient's clinical improvement.<sup>13,14,19</sup> When combined with other systemic drugs, the variable doses of CsA ranged from 1 to 8 mg/kg/day.<sup>12,15-18</sup> In particular, CsA in combination with corticosteroids, either in continued dose (hydrocortisone hemisuccinatum 200 mg/day; prednisolone 1.5 mg/kg/day; and dexamethasone 1 mg/kg/day)<sup>12,13,15</sup> or pulsed dose (methylprednisolone 30 mg/kg/day for 3 days) was given to three patients.<sup>16,17</sup> No mortality was reported in all cases. CsA monotherapy or in combination with other drugs led to the immediate arrest of the disease progression (1-5 days) and accelerated complete re-epithelialization (11-15 days). The use of CsA in combination with other immunosuppressive drugs seemed to lead to faster overall clinical improvement compared with CsA monotherapy.

With the first one published by St. John *et al.*,<sup>13</sup> this study was the second report on the successful use of CsA in combination with a continued dose of methylprednisolone for pediatric SJS/TEN.



**Figure 2.** Timeline of the course of the disease and therapies. CPM, chlorpheniramine maleate; PCM, paracetamol.



**Table 1.** Summary of published cases on the use of cyclosporine for treating pediatric epidermal necrolysis.

Author	Year	Age	Sex	Cause	BSA %	Dose of CsA	Other systemic therapies	Response (days after CsA administration)	Outcome
Szeptietowski <i>et al.</i> <sup>15</sup>	1997	8yo	F	Carbamazepine, Acetyl-salicylic acid	100	8 mg/kg/d 21d	Supportive care Doxycycline hydrochloride Hydrocortisone hemisuccinatum 200 mg/d	Sign of re-epithelialization within 14d	Survived
Aihara <i>et al.</i> <sup>16</sup>	2007	10yo	F	Unidentified	>30	1 mg/kg/d	Supportive care Methylprednisolone 30 mg/kg/d 3d	Progression stopped within 24h Visible improvement of erythema within 3d Complete re-epithelialization within 14d	Survived
St. John <i>et al.</i> <sup>13</sup>	2017	17 mo	M	Phenytoin	25	3 mg/kg/d bid 7d	Supportive care Prednisolone 1.5 mg/kg/d	Progression stopped within 2d Visible improvement of erythema within 4d Near complete re-epithelialization within 10d	Survived
		5yo	M	Acetaminophen	15	3 mg/kg/d bid 8d 1.5 mg/kg/d 7d	Supportive care	Progression stopped within 3d Complete re-epithelialization within 15d	Survived
		8yo	F	Unidentified	15	3 mg/kg/d bid 3d 1 mg/kg/d 2d 3 mg/kg/d 7d 1.5 mg/kg/d 7d	Supportive care	Progression stopped within 2d Complete re-epithelialization within 14d	Survived
Sato <i>et al.</i> <sup>17</sup>	2018	11yo	F	Clarithromycin	90	4 mg/kg/d 5d	Supportive care Methylprednisolone 30 mg/kg/d 3d IVIg 2 g/kg/d 2d Plasmapheresis	NA	Survived
Zielińska <i>et al.</i> <sup>18</sup>	2018	8yo	F	NA	90	3 mg/kg/d 20d	Supportive care IVIg 2 g/kg/d 5d Plasma exchange	NA	Survived
Coulombe <i>et al.</i> <sup>12</sup>	2019	17yo	M	Carbamazepine	45	3 mg/kg/d 7d 1.5 mg/kg/d 7d	Supportive care Dexamethasone 1 mg/kg/d 3d Etanercept 0.8 mg/kg 1 dose	Progression stopped within 5d Complete re-epithelialization within 12d	Survived
Alajmi <i>et al.</i> <sup>14</sup>	2020	11yo	F	Carbamazepine	20	3 mg/kg/d bid 15d 2 mg/kg/d 3d 1 mg/kg/d 3d	Supportive care	The lesion resolved within 7d Complete re-epithelialization within 11d	Survived
Quintana-Castanedo <i>et al.</i> <sup>19</sup>	2021	10yo	M	Lamotrigine	40	4 mg/kg/d 10d	Supportive care Corticosteroid 1-2 mg/kg/d (prior)	Progression stopped within 4d Partial re-epithelialization within 10d	Survived
Our case	2022	8yo	M	MParacetamol, chlorpheniramine, antibiotic (?), 15	15	2.5 mg/kg/d	Supportive care	Progression stopped within 24 h	Survived

F, female; M, male; yo, years old; mo, months; h, hours; d, days; BSA, body surface area; CsA, cyclosporine A.

For our patient, an initial dose of 2 mg/kg/day methylprednisolone was given with CsA at 2.5 mg/kg/day on day 6. Clinical improvement was evident within 24 hours. This finding demonstrated that CsA addition, even past the onset of SJS/TEN, is still beneficial to halt the disease progression, thus supporting the report of Quintana-Castaneda *et al.*<sup>19</sup> This phenomenon may be partly explained by the synergistic effects of both drugs in the treatment of SJS/TEN. High-dose corticosteroids possess potent anti-inflammatory effects by suppressing enzymes and pro-inflammatory cytokines, such as IL-1, IL-6, and TNF $\alpha$ , which are the leading culprits of inflammation.<sup>20</sup> By contrast, cyclosporine has a specific effect on T cells by inhibiting calcineurin, which downregulates IL-2, the primary cytokine necessary for full T-cell activation.<sup>21,22</sup> Hence, combining both drugs may be beneficial in controlling SJS/TEN, particularly with patients unresponsive to standard treatment.

No guideline on the correct dose of CsA for SJS/TEN has been established, even in adult patients. The typical dose is 2.5-5 mg/kg/day for 7-10 days, followed by gradual tapering. According to previous reports, the CsA dose administered in children was between 1 and 8 mg/kg/day, and no side effects were observed. Because of its vasoconstrictive effect, CsA is most commonly associated with hypertension and renal damage.<sup>23</sup> However, these conditions are not seen in short-term CsA therapy. Furthermore, previous reports showed that CsA is well tolerated, even by critically ill patients.<sup>23,24</sup> No studies have determined differences in the administration of CsA between adults and children for SJS/TEN treatment. Some researchers revealed that children might need a high dose of CsA due to individual variabilities of biological maturation, including high CsA metabolism and low absorption.<sup>25</sup> Even with the clinical benefits and good safety profile of CsA, the mainstay of management should focus on early diagnosis, discontinuation of drugs, and supportive therapy for SJS/TEN overlap syndrome.

## Conclusions

This case report highlights the benefit of adding CsA to supportive care and systemic therapy such as corticosteroids for the treatment of pediatric SJS/TEN overlap syndrome. CsA is beneficial as monotherapy and in combination with other drugs. Here, CsA combined with corticosteroids is useful to quickly arrest the disease progression possibly due to the synergistic effects of both drugs. Moreover, CsA is reportedly well tolerated with minimal side effects. Clinical studies are warranted to further assess the efficacy and safety of CsA for treating SJS/TEN in children.

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