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# Toxic Epidermal Necrolysis Treated with Intravenous Immunoglobulin and Granulocyte Colony-Stimulating Factor

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*We report a case of toxic epidermal necrolysis who was successfully treated with intravenous immunoglobulin and granulocyte colony-stimulating factor. He had poor prognostic factors such as extensive epidermal loss, neutropenia, acute respiratory distress syndrome and Candida sepsis, but nonetheless made a complete recovery.*

**Key words:** *G-CSF, Immunoglobulin, Toxic epidermal necrolysis.*

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## Introduction

Toxic epidermal necrolysis (TEN) is a severe drug-induced life-threatening disease and characterized by fulminant and widespread blisters responsible for epidermal sloughing(1). It is associated with high mortality and the majority of the patients die from complications of infection(1). Supportive therapies and antiseptics are used in patients with TEN. Different drugs such as cyclophosphamide, pentoxifylline, thalidomide, cyclosporine and plasmapheresis have been reported to be useful in single case observations(1). Recently, a few cases have been treated with human intravenous immunoglobulin (IVIG)(2-4). Here, we report a case of TEN treated with IVIG and granulo-

cyte colony-stimulating factor (G-CSF) successfully.

## Case report

A 2-year-old boy was admitted to a local hospital for fever and cough, and diagnosed parapneumonic effusion and ampicillin-sulbactam was begun. Four days later, he was referred to our hospital because of persisting fever. On physical examination, the right hemithorax was dull to percussion, and breath sounds were decreased and diffuse crackles were heard. Hemoglobin was 7.4 g/dL, white blood cell count 19400/$mm^3$, platelet count 939000/$mm^3$. Erythrocyte sedimentation rate was 40 mm/h and C-reactive protein 13.4 mg/dL. The chest *X*-ray showed opacity on the right hemithorax, left side displacement of mediastinum. Exudative pleural fluid was obtained by thoracentesis and culture was negative. He was hospitalized and managed with teicoplanin (10 mg/kg i.v., once daily) and chest tube drainage. After two weeks, amikacin was added to the therapy (15 mg/kg i.v, once daily) because of spiking fever. On the 24th day, erythematous rashes developed on his face and trunk (*Fig. 1*). It was though as drug reaction and teicoplanin and amikacin was changed to meropenem (80 mg/kg three times a day). Hemoglobin was 7.5 g/dL, white blood cell count 6700/$mm^3$; platelet count 365000/$mm^3$. Liver and kidney function tests were normal. Antihistaminic was added to the therapy but did not prevent the occurrence of blisters. Parenteral prednisolone (2 mg/kg/day-totally 30 mg) was started. One day later, his condition worsened, mucocutaneous detachment and erythema started and effect 90% of the skin surface and oral and genital mucous membranes. Nikolsky's sign was positive on the lesions and normal skin. Arterial blood gas analysis revealed hypoxemia. The chest *X*-ray showed bilaterally diffuse pulmonary opacities suggesting acute respiratory distress syndrome (ARDS). The patient was placed on an airy bed and benefited from supportive and antiseptic measures including daily baths. Prednisolone was stopped and IVIG (Sandoglobulin®, Novartis) was administered twice at a dose of 0.5 g/kg per day (totally 37, 5 g) for 5 consecutive days. A skin biopsy showed full-thickness epidermal necrolysis and sub-sepidermal blisters with presence of rare mononuclear cells scattered between necrotic keratinocytes. Candida albicans was obtained on blood culture and amphotericin B was added to the therapy. Two days later, white blood cell decreased to 1800/$mm^3$ (absolute neutrophil count 600/$mm^3$) and G-CSF (Neupogen®) was added to the therapy (5 µg/kg/day, subcutaneously-totally 375 $\mu$g) for six days.

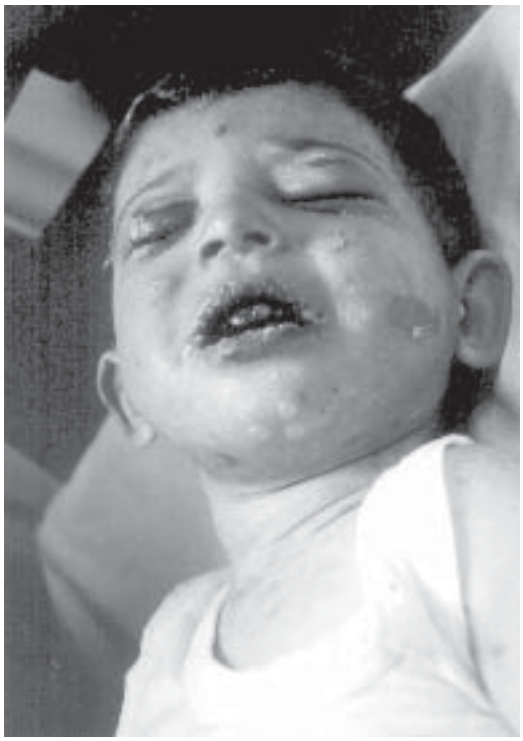

*Fig. 1. Initial skin involvement; erythematous rashes and blisters on the face and trunk.*

Two days later, new blisters did not develop and resolved within 10 days. The cutaneous alterations improved and erythematous rash vanished in two weeks. The re-epithelialization was completed within one month. The patient recovered satisfactorily.

## Discussion

Toxic epidermal necrolysis is characterized by rash, bullae and diffuse exfoliation of wide cutaneous surface areas that is mostly observed secondary to drugs such as co-trimoxazole, anticonvulsant and nonsteroidal anti-infalmmatory analgestic(5). In our case, teicoplanin and amikacin were the possible provocative agents. There was not any proven circulating bacterial toxin in our case, also the pattern of eruptions did not fit to erythema multiforme, and epidermal detachment was affecting 90% of the total body area, therefore we rule out other vesiculobullous diseases. The pathological examination was also confirming the diagnosis of TEN.

The precise pathomechanisms of TEN remain unknown. It has been purposed that drugs or their metabolities act as haptens and render keratinocytes antigenic by binding their surface(6). Immunohistological studies on cutaneous biopsies of the patients affected by early stage of TEN have shown a widespread dermal infiltrate in dermal-epidermal junction, suggesting a cytotoxic cell mediated reaction versus keratinocytes(6). This cell-mediated immune response leads to keratinocyte death by apoptosis, involving CD95 (Fas) cell surface receptor ligand system(6,7). Fas ligand system is normally expressed on keratinocytes and up regulated by cytokines and skin infiltrating immune competent cells(8). In TEN, keratinocytes express large amounts of lytically active Fas ligand that induces apoptosis of Fas + cells as keratinocytes(7). IVIG involves the inhibition of Fas mediated keratinocyte apoptosis by Fas blocking antibodies contained in IVIG preparation and also it decreases life-threatening infections. We used IVIG in our patient 24 hours later after the appearance of first skin lesions. Two days later, epidermal detachment was interrupted and complete skin re-epithelialization was completed within the two weeks. We think that poor prognostic factors were delayed the skin re-epithelialization in our patient.

Neutropenia is regarded as negative prognostic factor(9). In our case, neutropenia was related with bone marrow suppression caused by teicoplanin, amphotericin B and sepsis. The neutrophil count recovered to normal level within six day after G-CSF administration. Pulmonary involvement is another poor prognostic factor and occurs in 25% in TEN(10). It may occur as a result of mucosal sloughing of the tracheobronchial tree.

As a result, our patient had excellent outcome with IVIG and G-CSF added to basic symptomatic therapy, despite the poor prognostic factors. Even though, we could not show CD95 receptor disappearance by immunohistological methods during the therapy, we though that the successful recovery was related with IVIG, IVIG must be at the top of the list in infants for the treatment, because of severe and diffuse mucocutaneous detachment as in our case is a risk factor for sepsis, and also G-CSF must be added to the therapy when the neutropenia is present.

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# Acute Renal Tubular Dysfunction in Association with *Salmonella enteritidis*

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*A 13-year-old boy presented with acute renal tubular dysfunction after an infection with salmonella enteritidis. The child recovered following treatment with ciprofloxacin for a week.*

**Key words:** *Nephritis, Renal, Salmonella.*

Tubular dysfunction and acute tubulo-interstitial nephritis (AIN) have been described secondary to drugs, toxins as well as infections(1). Salmonellosis has been associated with immune glomerulonephritis, bacteremia or pyelonephritis(2). AIN secondary to *Salmonella typhimurium* has been reported in a 12-year-old girl(3) and adults(4,5) either in isolation or with schistosomiasis.

We describe a child with acute tubular dysfunction after an infection with *Salmonella enteritidis.*

## Case Report

A 13-year-old boy presented with diarrhea and vomiting of 3 days duration associated with fever and generalized malaise. There was

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