

**Figure 1.** A) Pustules with desquamation and erythema on the hand and foot. B) Histological examination reveals hyperkeratosis, elongation of the rete ridges, and extensive neutrophilic infiltration with spongiform pustules below the stratum corneum (haematoxylin-eosin [H&E]; original magnification: x40). C) Painful erythematous plaques on the leg. D) Histological examination reveals septal panniculitis without evidence of vasculitis (H&E; original magnification: x40).

pathogenesis of EN [5]. In support of these findings, it has been reported that TNF- $\alpha$  inhibitors are effective for idiopathic [6] or IBD-associated EN [5]. Further study will be required to clarify the pathogenesis of TNF- $\alpha$  inhibitor-induced EN.

In the present case, psoriasis and EN were elicited by each different TNF- $\alpha$  inhibitor. A recent study has shown that TNF- $\alpha$  inhibitor-induced paradoxical psoriasis is linked to specific IL-23 receptor gene polymorphisms [1]. Furthermore, a correlation between sarcoidosis-associated EN and polymorphism in the TNF- $\alpha$  promoter region has been reported [4]. Further study of such paradoxical reactions is needed to avoid any undesirable withdrawal of treatment and to establish personalized treatment for individual patients. ■

**Disclosures.** *Conflicts of interest: none.*

Department of Dermatology, Iwate Medical University School of Medicine, 2-1-1, Idaidori, Yahaba-cho, Iwate 028-3695, Japan <dwatabe@iwate-med.ac.jp>

Daisuke WATABE  
Hiroo AMANO

1. Garcovich S, De Simone C, Genovese G, Berti E, Cugno M, Marzano AV. Paradoxical Skin Reactions to Biologics in Patients with Rheumatologic Disorders. *Front Pharmacol* 2019; 10: 282.

2. Naranjo CA, Busto U, Sellers EM, *et al.* A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30: 239-45.

3. Delle Sedie A, Bazzichi L, Bombardieri S, Riente L. Psoriasis, erythema nodosum, and nummular eczema onset in an ankylosing spondylitis patient treated with infliximab. *Scand J Rheumatol* 2007; 36: 403-4.

4. Rosen T, Martinelli P. Erythema nodosum associated with infliximab therapy. *Dermatol Online J* 2008; 14: 3.

5. Gilchrist H, Patterson JW. Erythema nodosum and erythema induratum (nodular vasculitis): diagnosis and management. *Dermatol Ther* 2010; 23: 320-7.

6. Ortego-Centeno N, Callejas-Rubio JL, Sanchez-Cano D, Caballero-Morales T. Refractory chronic erythema nodosum successfully treated with adalimumab. *J Eur Acad Dermatol Venereol* 2007; 21: 408-10.

doi:10.1684/ejd.2021.4058

## Therapeutic plasma exchange combined with continuous venovenous hemofiltration in a series of pediatric patients with toxic epidermal necrolysis

Toxic epidermal necrolysis (TEN), characterized by widespread epidermal necrosis of skin and mucosa, is a

rare, fulminating, and life-threatening disorder in adults and children [1]. While in adults, non-pharmacological extracorporeal detoxification including plasmapheresis (therapeutic plasmatic exchange, TPE) and/or continuous venovenous hemofiltration (CVVHF) are used with promising results in refractory disease, limited clinical evidence supports the efficacy of these therapies in children [2, 3]. Here, we present our experience using TPE combined with CVVHF in pediatric patients with TEN.

We reviewed three sequential pediatric patients diagnosed with TEN who received extracorporeal detoxification at our institution between 2016 and 2019. All patients were male, 14 to 44 months old, initially hospitalized for pneumonia, where they received intravenous antibiotics (*figure 1*). Cutaneous rash developed within one to seven days from the initiation of the antibiotic treatment and further transformed in the following days into confluent maculopapular exanthema with blisters and denudation of the epidermis in large patches. Patients were transferred to intensive care where, in addition to withdrawing the antibiotics and supportive systemic therapy, intravenous methylprednisolone (2 mg/kg/d) and IVIG (1 mg/kg/d) were administered. Despite pharmacologic intervention, their condition deteriorated. All three patients developed multiple erosive lesions affecting the oropharyngeal, anal, and ocular mucosa. TEN was deemed to be refractory to the supportive and steroid treatment, and combined extracorporeal therapy, TPE and CVVHF was initiated (*see supplementary material*).

The number of TPE sessions varied between three and four, and the duration of CVVHF varied from 120 (5.0) to 202 (8.4 days) hours. The time from the start of extracorporeal therapy to peak denudation ranged between two and five days. The interval from peak denudation to reepithelialization was seven and 12 days for Patients 1 and

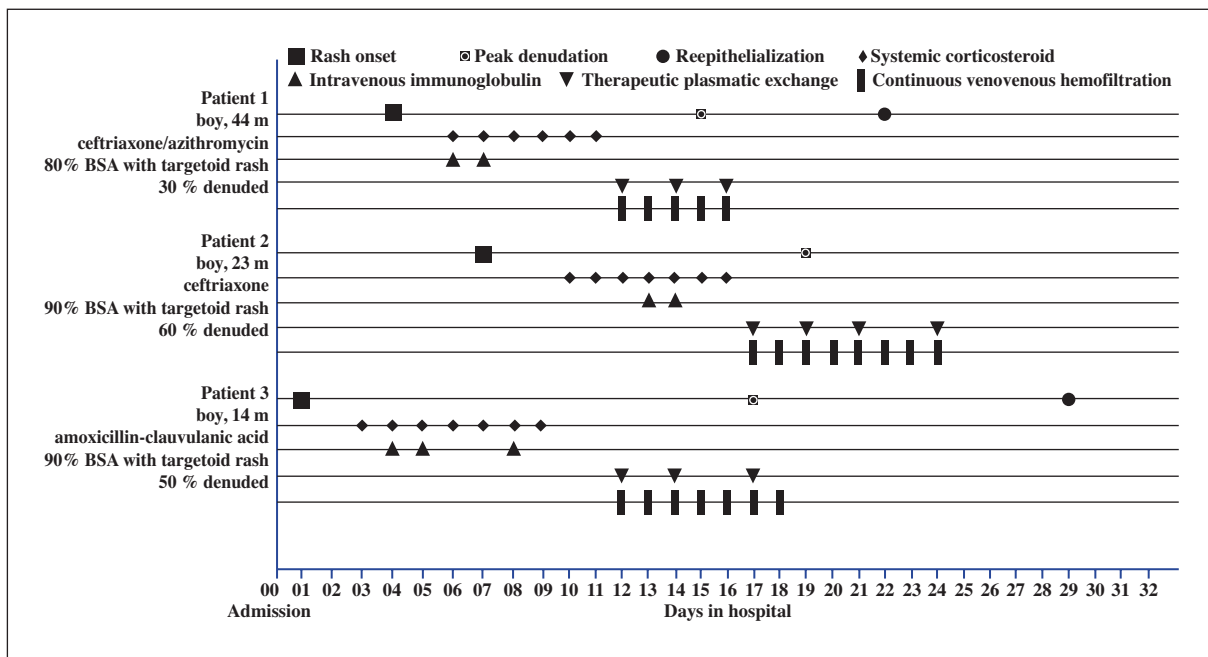
3, respectively. Unfortunately, Patient 2 developed septic shock on Day 26 and died on Day 32. *Acinetobacter baumannii* was detected in both wound swab and blood cultures. Patient 1 had a 33-day hospital stay without any further complications, whereas Patient 3 required oxygen therapy and had a 98-day stay.

The optimal management of pediatric TEN has not been established. To the best of our knowledge, this study is the first to examine the efficacy of combined extracorporeal detoxification therapy on severe and refractory pediatric TEN. Our rationale in adopting the extracorporeal therapy was based on the following:

- i) although the condition is considered immunologically mediated, there are also arguments in favor of a toxic mechanism [4];
- ii) plasmapheresis–TPE is a blood purification method that has shown rapid and dramatic improvement in adult patients with TEN (2,4);
- iii) CVVHF effectively regulates not only the volume, acid-base, and electrolyte balance, but also inhibits inflammatory cascade reactions, present in TEN [5];
- iv) other mediators, including granulysin, Fas ligand, TNF- $\alpha$ , and perforin/granzyme B, considered potential pathogenic factors of TEN, can be removed by CVVHF [6].

These methods ensure removal of pathogenic factors, the etiologic drug and its metabolites, as well as other unknown toxic substances that may be released in TEN.

We observed that within two to five days after administration of TPE combined with CVVHF, the progression of epidermal detachment was halted, and no new lesions developed in our patients. Under the treatment with



**Figure 1.** Timeline of hospital courses of treatment. The gender, age, implicated drug, and percentage of body surface area (BSA) affected are listed for each case. Patient 1 had a 33-day hospital stay without any further complications, whereas Patient 3 required oxygen therapy and had a 98-day stay. Patient 2 died from uncontrolled septic shock on Day 32.

TPE combined with CVVHF, our patients exhibited a remarkable time interval from peak denudation to re-epithelialization, which ranged from seven to 12 days. The number of TPE sessions and the duration of CVVHF varied among individuals, based on the clinical response to the treatment. Considering that the natural history of TEN may vary significantly and that our data was based on a small series of patients, one may argue that the beneficial effect of extracorporeal detoxification may have been a chance phenomenon. However, we believe that the extracorporeal treatment was effective because all our patients had severe conditions and their disease was refractory to conventional pharmacologic therapies and responded promptly to TPE combined with CVVHF.

It is our opinion that TPE combined with CVVHF therapies may be considered as an alternative treatment for severe pediatric TEN, especially when the treatment with steroids and IVIG fails. We acknowledge that more experience and research is needed before generalizing these therapies in children.

## Supplementary material

Supplementary material associated with this article can be found in the online version, at doi:10.1684/ejd.2021.4042. Details about the therapeutic plasma exchange (TPE) combined with continuous venovenous hemofiltration (CVVHF) are described as follows:

For this type of treatment, central vascular access was gained through the subclavian or femoral vein using a double-lumen catheter. For the TPE, plasma was obtained by centrifugation and separation from blood cells with the use of a spectra continuous separator (Gambro Renal Products, Meyzieu, France). On each exchange, the circulating plasma was replaced with a plasma substitute, obtained by combining fresh frozen plasma and albumin 5% at a flow rate between 3-5 mL/kg/min. The volume of plasma exchange was about 1 to 1.5-fold relative to the volume of circulating plasma, calculated using the formula:  $[\text{weight (kg)} / 13 \times (1 - \text{HCT} / 100) \times 1000]$  (HCT, hematocrit [in %]). The original blood cell components were returned to the patients. TPE was carried out every 2-3 days and the number of sessions was dependent on patient responsiveness and the extent of the disease.

CVVHF was performed over several consecutive days, but was suspended during the TPE course and immediately restarted after TPE was completed. CVVHF was performed using the Prismaflex monitor equipped with HF 60/100 filters and AN69 poly membrane that removed both solutes and fluid at a flow rate of 3-5 mL/kg/min. The replacement fluid was infused at 35-50 mL/kg/h in a post-dilution mode. Anticoagulation was used in all cases by adjusting an unfractionated heparin infusion to maintain activated partial thromboplastin time, two-fold higher than that for control (60-80 s). Discontinuation of TPE and CVVHF was dictated by the improvement in clinical outcomes, when the detachment of the epidermis was halted, and no further new lesions developed.

**Acknowledgments and disclosures.** Funding: this research was partially supported by the Modern Western Medicine

Guiding Project of the Shanghai Municipal Committee of Science and Technology (17411968900). Acknowledgments: none. Conflicts of interest: none. Informed consent: informed written consent (in Chinese) was obtained from the patients' parents.

<sup>1</sup> Department of Critical Care Medicine, Shanghai Children's Hospital, Shanghai Jiao Tong University, Shanghai 200062, China

<sup>2</sup> Institute of Pediatric Critical Care, Shanghai Jiao Tong University, Shanghai 200062, China

<sup>3</sup> Department of Obstetrics & Gynecology, Queen Elizabeth II Hospital, Alberta, Canada

<sup>4</sup> Department of Respiratory Medicine, Shanghai Children's Hospital, Shanghai Jiao Tong University, Shanghai 200040, China  
<dingguodong@shchildren.com.cn>  
<zyucai2018@163.com>

Yun CUI<sup>1</sup>  
Jingyi SHI<sup>1</sup>  
Chunxia WANG<sup>1,2</sup>  
Angela VINTURACHE<sup>3</sup>  
Guodong DING<sup>4</sup>  
Yucai ZHANG<sup>1,2</sup>

1. Dodiuk-Gad RP, Chung WH, Valeyrie-Allanore L, Shear NH. Stevens-Johnson syndrome and toxic epidermal necrolysis: an update. *Am J Clin Dermatol* 2015; 16(6): 475-93.

2. Egan CA, Grant WJ, Morris SE, Saffle JR, Zone JJ. Plasmapheresis as an adjunct treatment in toxic epidermal necrolysis. *J Am Acad Dermatol* 1999; 40(3): 458-61.

3. Bai M, Yu Y, Huang C, et al. Continuous venovenous hemofiltration combined with hemoperfusion for toxic epidermal necrolysis: a retrospective cohort study. *J Dermatolog Treat* 2017; 28(4): 353-9.

4. Chaidemenos GC, Chrysomallis F, Sombolos K, Mourelou O, Ioannides D, Papakonstantinou M. Plasmapheresis in toxic epidermal necrolysis. *Int J Dermatol* 1997; 36(3): 218-21.

5. Bellomo R, Tipping P, Boyce N. Continuous veno-venous hemofiltration with dialysis removes cytokines from the circulation of septic patients. *Crit Care Med* 1993; 21: 522-6.

6. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: part I. introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis. *J Am Acad Dermatol* 2013; 69(2): 173.e1-13; quiz 185-6.

doi:10.1684/ejd.2021.4042

## Considerations on SARS-CoV-2 vaccines in patients with autoimmune blistering diseases

Patients affected by autoimmune bullous diseases (AIBDs) are fragile due to immunosuppressive treatment. Infections, favoured by immunosuppression, represent an important cause of death in AIBD patients [1]. No specific dermatological guidelines address the SARS-CoV-2 vaccination issue in AIBD patients [1]. According to general guidelines for AIBD management, patients receiving immunosuppressive therapy should receive non-live