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Reconstructive

Management of Toxic Epidermal Necrolysis with Plasmapheresis and Cyclosporine A: Our 10 Years' Experience

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Background: The management of toxic epidermal necrolysis (TEN) is controversial and there is no uniform strategy.
Objective: To share our 10 years' experience in treating severe TEN with a novel protocol based on the association of cyclosporine A and plasmapheresis.
Methods: In this case series, we retrospectively collected and assessed the 12 cases of severe TEN treated from 2005 to 2015 at the Burn Unit of the University of Bari Policlinico hospital.
Results: Average body surface area was 77; average SCORETEN was 4.3. The 12 patients had been treated with culprit drug withdrawal, systemic corticosteroids, and/or cyclosporine A with no response. The protocol was successfully administered in all 12 cases. Average time to response from protocol start was 4.9 days. Average time to remission from protocol start was 22 days; average hospital stay at our unit was 24.8 days. Four patients developed severe complications; 1 patient died. No complications linked to the protocol therapeutic measures were observed. The relatively small number of cases given the rarity of the condition is a limitation of this report.
Conclusion: Our protocol based on the association of cyclosporine A and plasmapheresis is safe and efficacious in treating severe TEN. *(Plast Reconstr Surg Glob Open 2017; 5:e1221; doi: 10.1097/GOX.0000000000001221; Published online 22 February 2017.)*

Toxic epidermal necrolysis (TEN) is an acute disease characterized by severe necrosis of the skin that also manifests systemic symptoms. It is nowadays considered one end of a disease spectrum comprising Steven Johnson syndrome (SJS). It is rare, especially in children, and prompt management is essential for a favorable outcome.[1–3] The estimated incidence of TEN is 0.4–1.2 cases per million per year, with an overall annual risk in the general population of 0.93.[2] Although idiopathic and postinfectious forms have been described, SJS/TEN are mostly adverse drug reactions. Antibacterial and anticonvulsants are frequently referred as causing SJS and TEN, followed by analgesics and nonsteroidal anti-inflammatory drugs.[1–3] The mechanism leading to the development of lesions is not fully known; the main role is attributed to dysfunction of T lymphocytes.[4,5]

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Clinically, TEN is characterized by raised, blistered, and erythematous patches and/or plaques, which evolve rapidly to extensive areas of skin necrosis with loss of sheets of epidermis. In some affected patients, an acute sunburn-like appearance with evolution into extensive epidermal necrosis is seen. Nikolsky's sign is present (slight rubbing on apparently healthy skin results in exfoliation/lesion development). Skin biopsy shows that the level of separation is subepidermal and it is accompanied with overlying epidermal necrosis.[6] The mortality, ranging from 10% to 70%,[1,2] predominantly results from severe complications of multiple organ failure and infections affecting extensive areas of inflamed skin.

No uniform strategy of management has been established. Immunoglobulins and corticosteroids are the most reported therapies, although the efficacy of such treatments is controversial.[5,7,8] Immunosuppressive therapy with cyclosporine A (CsA) or infliximab can be considered.[7,8] An alternative method enabling the elimination of toxic and immunological factors is plasmapheresis.[7–9]

CASE SERIES

From 2005 to 2015 we treated 12 cases of severe TEN at the Burn Unit of the University of Bari Policlinico hos-

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pital. The characteristics of the 12 cases are summarized in Table 1. The average age was 35.9 years (51.7 excluding the 4 pediatric cases); half of the patients were men; the average body surface area (BSA) was 77; the average score of toxic epidermal necrolysis (SCORETEN) was 4.3, with a predicted mortality rate of 58.3%; 4 patients presented severe mucosal involvement, defined as combined and diffuse respiratory, gastroenteric, genital, and ocular involvement. All patients showed systemic symptoms, such as fever, asthenia, pain, and dyspnea. Blood examinations varied, but common findings included lymphopenia (selective depletion of CD4 as evidenced by lymphocytogram), mild thrombopenia, liver and pancreatic enzymes increase, hypoproteinemia, albuminuria, and increased C reactive protein (average: 82 mg/L). Histological examination, performed in each case, confirmed the diagnosis (Fig. 1). Etiology varied, but mainly comprised antibiotics and nonsteroidal anti-inflammatory drugs. First-line therapy, defined as identification and withdrawal of the culprit medication, had been carried out in each patient. Also, the 12 patients had all been previously treated, before a definition of TEN (BSA <30%) with early systemic corticosteroids with no response; 4 of them had undergone combination or sequential therapy with corticosteroids and cyclosporine A with no success. At our unit, all previous therapies were discontinued and all patients were treated with a novel therapeutic protocol we devised (Table 2), introduced following a specific management flowchart (Fig. 2). The protocol was successfully administered in all 12 cases. The average time from initial disease presentation (first signs and symptoms) to first treatment (previous therapy) was 1.3 days, whereas the average time from initial disease presentation to treatment with our protocol was 4.6 days. Each step was introduced with an original timing. In particular, at day 1 of hospitalization in our unit CsA at full dosage (intravenous 250 mg/die or 4 mg/kg/die in pediatric patients) was introduced (the dose was adjusted in those 4 patients already under CsA). At day 3 daptomycin and plasmapheresis were introduced. CsA administration continued for 15 days, daptomycin for 10 days, plasmapheresis consisted of 7 cycles spaced by 2 days each. In the 3 cases that developed sepsis, meropenem (intravenous 1 g ×3/die in case 3; 40 mg/kg ×3/die in case 8 and 12) and fluconazole (intravenous 400 mg/die in case 3; 6 mg/kg/die in case 8 and 12) were administered.

Topical wound care started on the first day of admission, and included thorough detersion with chlorhexidine gluconate 5% solution and rinse with saline of the whole body, followed by application of petrolatum ointment to apparently healthy skin and methylprednisolone aceponate ointment on erythematous but intact skin. Blistering areas were aspirated if required, de-roofed, and then covered with Ag controlled release hydrofibers (Aquacell AG). The latter was left in place until spontaneous detachment occurred, and then replaced if necessary up to complete healing, whereas the other skin areas were dressed every 48 hours.

After an average of 9.2 days from protocol start, supportive measures were tapered. The average time to response, defined as halt of skin sloughing increase with

Table 1. Characteristics of Our Study Population and Therapeutic Results

Case	Age	Sex	Etiology	Previous Therapies	BSA	Severe Mucosal Involvement	SCORETEN (max 7)	Time from Initial Disease Presentation to First Treatment (d)	Time from Initial Disease Presentation to Protocol Start (d)	Time to Response from Protocol Start (d)	Time to Remission from Protocol Start (d)	Hospital Stay (d)	Complications	Follow-up (mo)
1	47	F	SULFONAMIDE	Cort, CsA	65		4	1	4	5	20	23		24
2	52	M	EUCALYPTOL (aerosol)	Cort	75		5	2	5	6	25	27		18
3	82	F	IBUPROFEN	Cort	100	x	7	1	6	NA	NA	NA	Sepsis/Septic shock /ARDS/ Exitus	NA
4	6	F	NIMESULID	Cort	100		4	1	4	NA	32	34	Interstitial pneumonia	16
5	51	F	CEPHALOSPORIN	Cort	70		4	2	4	4	20	22		20
6	55	M	ALLOPURINOL	Cort, CsA	80	x	5	2	6	6	22	24		24
7	65	M	CEPHALOSPORIN	Cort, CsA	75		4	1	5	5	18	20		9
8	2	F	AMOXICILLIN/ CLAVULANIC ACID	Cort	70		4	1	5	4	18	21	Sepsis/pancreatitis	18
9	24	M	DICLOFENAC	Cort, CsA	70	x	3	1	4	4	25	28		18
10	38	M	THIOCOLCHICOSIDE	Cort	80	x	5	2	6	6	26	29		12
11	6	F	KETOPROFEN	Cort	75		4	1	3	5	20	24		12
12	3	M	AMOXICILLIN	Cort	60		3	1	4	4	16	21	Sepsis	8

Time to response in case 3 and 4 could not be determined because BSA = 100.
BSA, body surface area; SCORETEN, score of toxic epidermal necrolysis; ARDS, acute respiratory distress syndrome; Cort, corticosteroids; CsA, cyclosporine A; NA, not applicable.

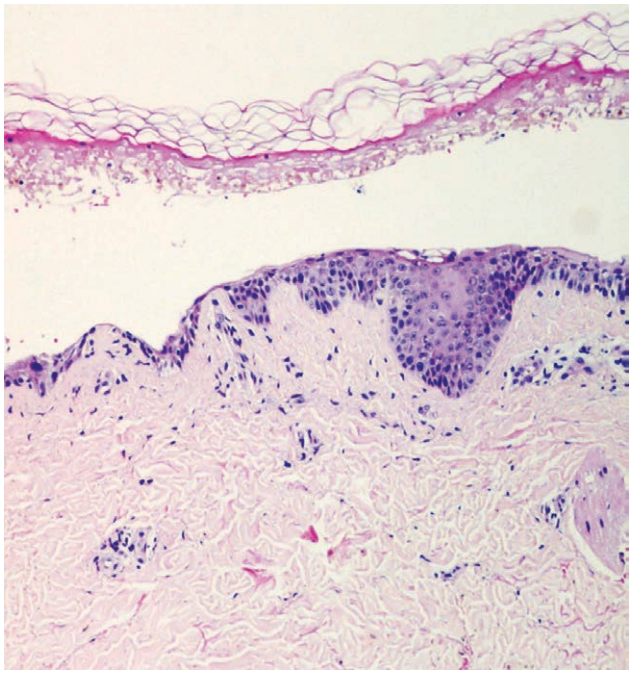

Fig. 1. TEN (hematoxylin and eosin). Notice the characteristic subepidermal detachment with full-thickness epidermal necrosis.

a Nikolsky's negative sign, and time to remission from protocol start (complete reepithelization) were, respectively, 4.9 and 22 days; the average hospital stay at our unit was 24.8 days. Four patients developed severe complications; 1 of these patients died (mortality rate 8.3%). No complications directly linked to the protocol therapeutic measures were observed. Figures 3–5 show case number 4 and 7 at time of admission at our unit, and at time of remission. After discharge, patients were scheduled for regular follow-up once every 15 days for the first month, and then once every 3–4 months. The average follow-up time was 16.2 months (min 8 – max 24).

DISCUSSION

The management of SJS and TEN is full of controversy and debate. The first obstacle is the difficulty of making an accurate diagnosis. Further, the precise pathophysiological mechanisms remain unclear. Authors agree only as to the strategy of management in the early stages. Such strategy involves early diagnosis, elimination of a causative factor, immediate institution of treatment, and transfer of patients to a specialist department. A decreased number of complications have been observed in individuals treated systemically, compared with the group treated supportively.[2,5,8] The methods of systemic treatment, however, require further studies to evaluate their efficacy. Evidence is even scarcer in children, as the bulk of the literature about management in SJS and TEN include only adults or adult series. Low numbers of pediatric patients and poor quality of the reports are responsible for a lack of standardization to classify and evaluate the prognosis and evolution of this group of patients.[3]

Table 2. The Therapeutic Protocol Administered in Our Cohort of Patients

Therapeutic				Supportive			
Immunosuppressive	Plasmapheresis	Antibiotics	Topical	Hydroelectrolytic	Metabolic	Ventilation	Pain control
Cyclosporine A 250 mg/die IV (4 mg/kg/die in pediatric patients) for 15 d	7 cycles (every 2 d)	Daptomycin 4 mg/kg/die for 10 days	Detersion with chlorhexidine gluconate 5% solution and saline Emollients (normal skin) Corticosteroids (erythematous skin) Ag controlled release hydrofibers (denuded skin, after blister de-roofing)	Isotonic saline Blood proteins	Parenteral/ enteral nutrition	Invasive Noninvasive	IV morphine Oral methadone

IV, intravenous.

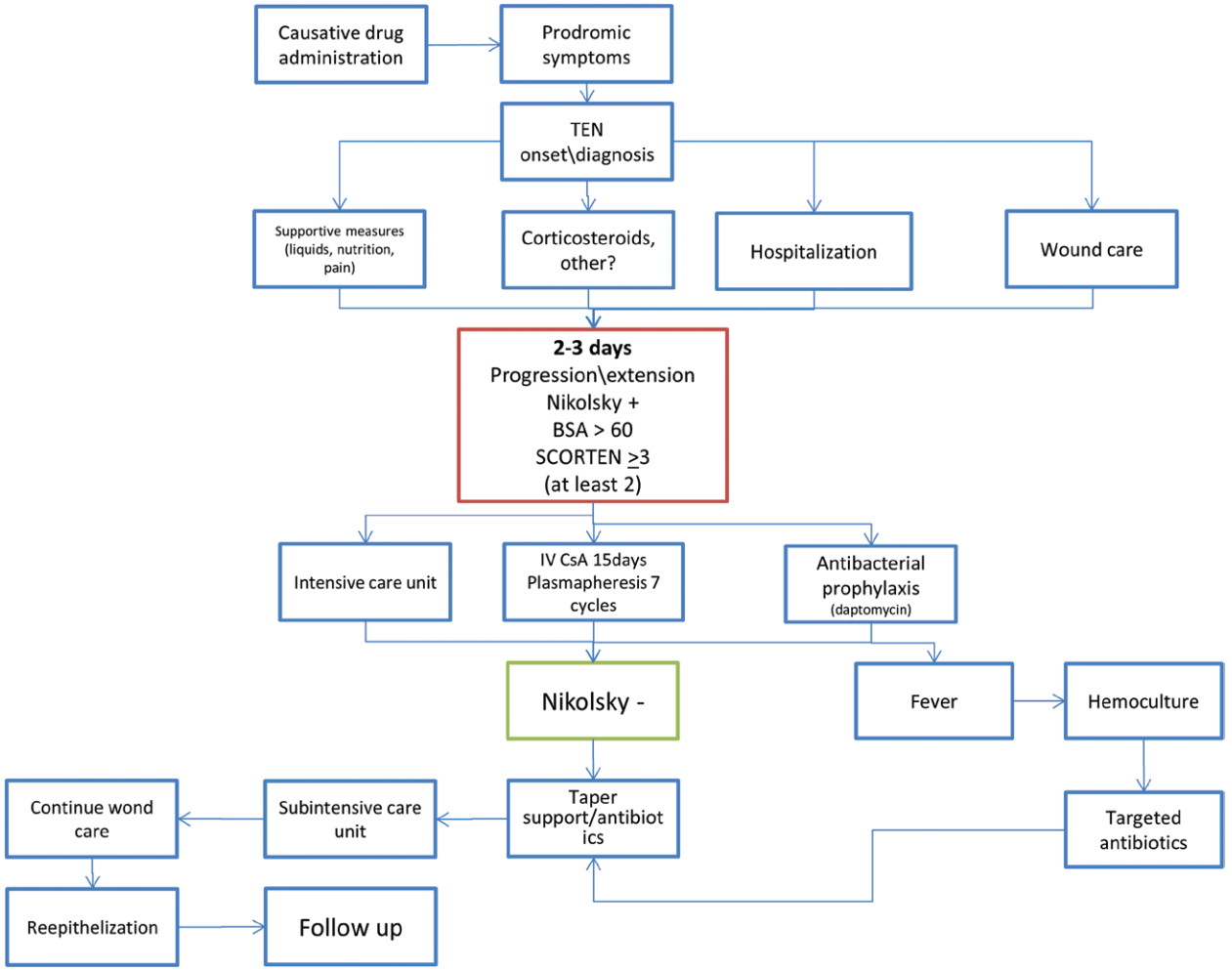

Fig. 2. Flowchart of our therapeutic management of TEN.

Topical wound care management is also far from standardized, ranging from topical immunosuppressants to epithelial substitutes and skin allografts.[10,11] A recent article by Abela et al[12] proposed a comprehensive wound care algorithm based on wound stage. Although our approach is similar on apparently healthy and erythematous skin areas, our personal experience in managing intermediate-superficial burns led us to prefer the use of hydrofibers in treating TEN denuded skin lesions, with satisfactory results and no need to resort to more expensive solutions. Of course comparative studies between different treatment modalities are currently lacking and would be much needed.

Finally, even though the standard SCORTEN has been validated as a prognostic indicator of mortality and morbidity in patients with SJS and TEN,[13] this has lacked clinical use in general and has only recently been assessed in children.[14]

We herein report our 10 years' experience in treating severe TEN. Over the years we developed our own personal protocol (Table 2), which we believe correctly addresses every key pathological aspect of TEN. In particular, such protocol comprises: hydroelectrolytic systemic re-equilibration with isotonic saline solution and blood proteins repletion; metabolic re-equilibration by means of parenteral or enteral nutrition; respiratory support with invasive or noninvasive ventilation as needed; systemic immunomodulation by administration of high-dose CsA; pathological immunogenic factors removal by plasmapheresis; prophylaxis and treatment of systemic infections by administration of daptomycin (6 mg/kg/die), which based on hemoculture can be associated to other antimicrobials; control of the wound bed using a single advanced dressing made of hydrofibers with Ag ions controlled release (Aquacell AG) over denuded skin and emollients and corticosteroids over apparently healthy and erythematous skin; and pain control with intravenous morphine, later substituted with oral methadone.

In our case series, the suspected drug already withdrawn, prednisone or a combination of prednisone and cyclosporine A, did not prove efficient enough to induce remission of the clinical condition (Figs. 3, 5A), and given the deteriorating evolution despite the undergoing therapy we undertook the decision to introduce plasmapheresis associated to high-dose intravenous CsA. This, together with the other supportive and topical therapies, produced a very precocious improvement in both systemic and cutaneous

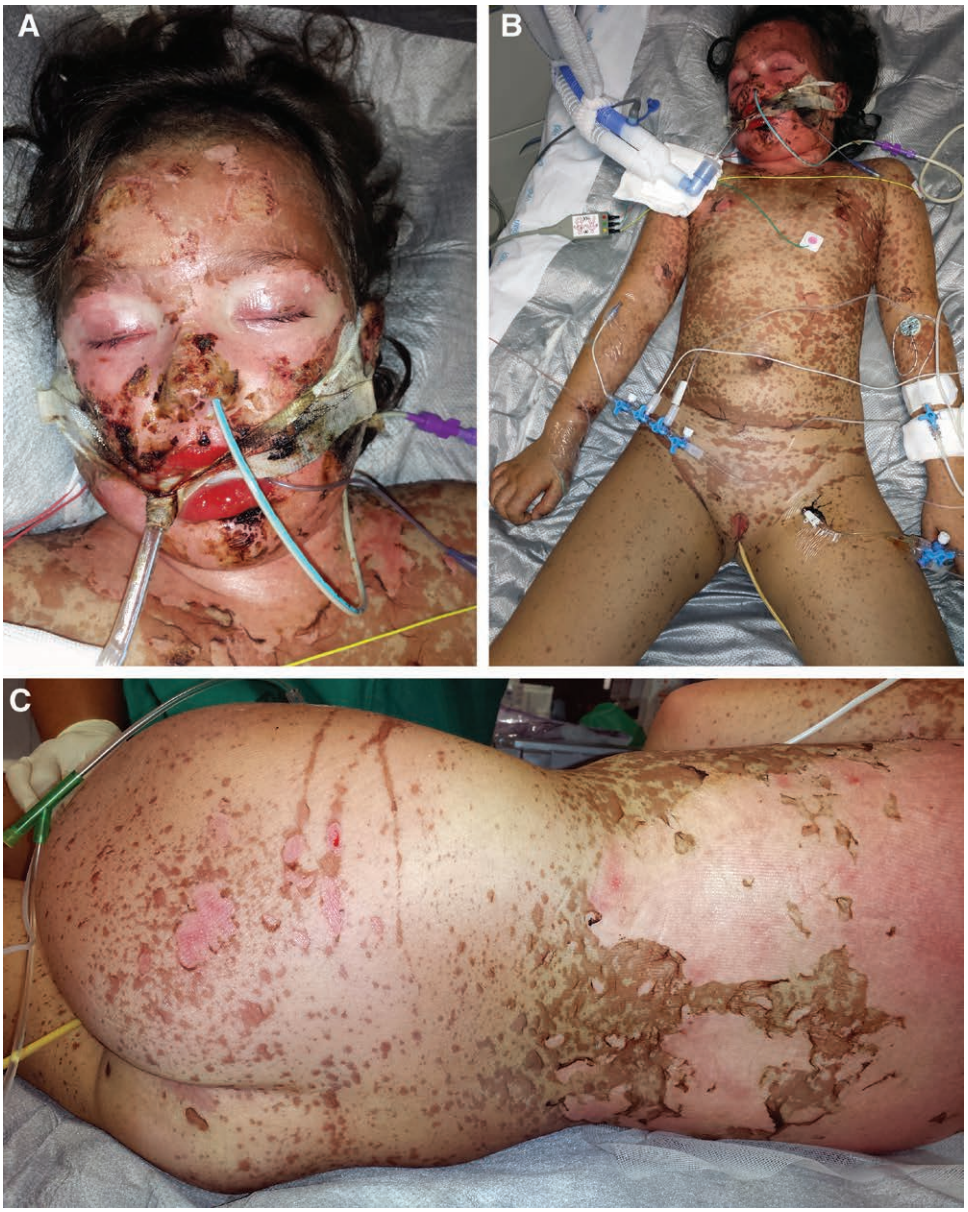

Fig. 3. TEN case number 4. Patient at time of admission to our unit. Notice the extensive BSA involved. A, Detail of the face. B, Anterior aspect. C, Posterior aspect.

signs (average time to response: 4.9 days), and effectively led to circulatory and respiratory stabilization with consequent patients discharge from the intensive care unit (average time to supportive measures tapering: 9.2 days). Skin lesion progression was halted, with no more sloughing increase and negative Nikolsky's sign, and they slowly started to heal, with complete reepithelization in 22 days average after protocol start (Table 2 and Figs. 4, 5B). In Figure 2, notice the 2 key points of our therapeutic flowchart. Firstly, after institution of hospitalization, first-line therapy, topical wound care and supportive measures (liquids, nutrition, and pain), the decision to proceed with transfer to intensive care unit and protocol start was dependent on a series of parameters. In particular at least 2 parameters had to be present among: clinical evidence of disease progression/extension, a positive Nikolsky's sign, a BSA >60, and a SCORTEN ≥3. The accompanying anti-Gram-positive prophylaxis was mandatory given the need for a central access to begin plasmapheresis. Only in cases of fever development, hemocultures were carried out and additional specific antibiotics administered. The second key point was when the Nikolsky's sign turned negative, an indication of disease progression halt. This resulted in the decision to taper supportive measures and antibiotics, and ultimately to transfer patients to the sub–intensive care unit. Topical wound care continued until complete reepithelization.

In our case series, 1 patient died of septic shock and acute respiratory distress syndrome. This patient had the highest SCORTEN of our cohort, reflecting her elderly age, her several comorbidities (among which a

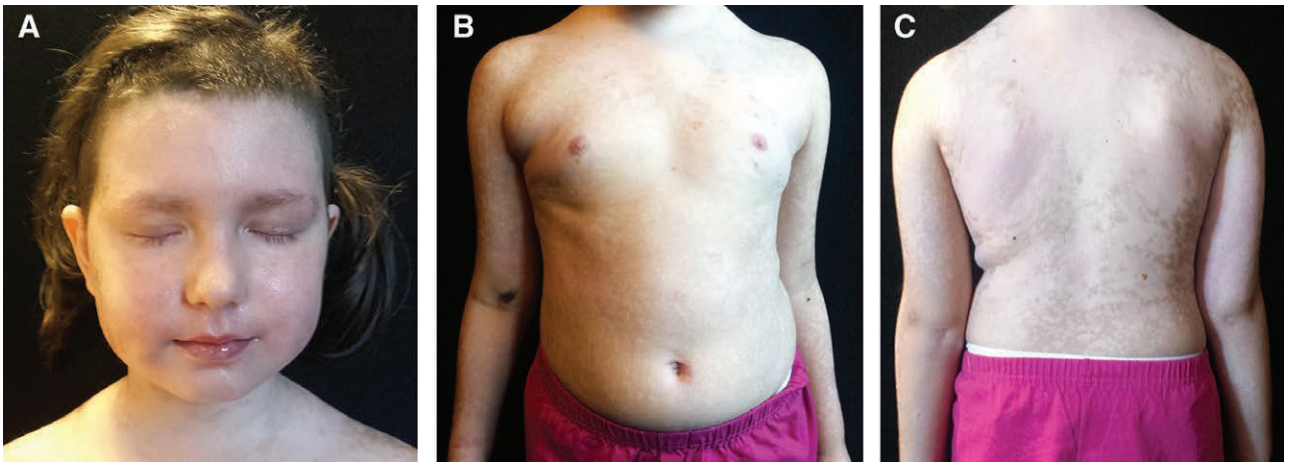

Fig. 4. TEN case number 4. Remission at 32 days from protocol start. A, Detail of the face. B, Anterior aspect. C, Posterior aspect.

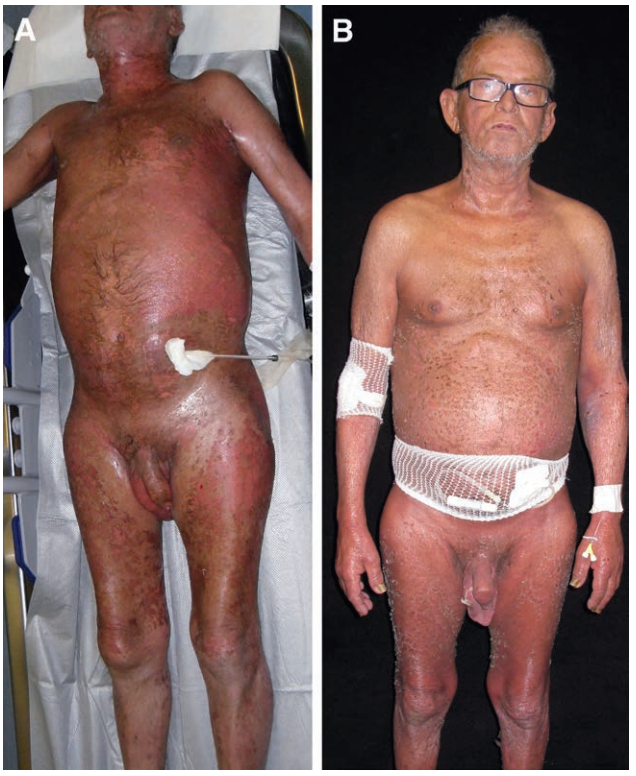

Fig. 5. TEN case number 7. A, Patient at time of admission to our unit. B, Remission at 18 days from protocol start. This patient showed a relatively quick remission and had the shortest hospital stay at our unit.

malignancy) and the BSA affected extension (100%). Of note, as reasonably expected, average time to remission and hospital stay in our cohort seemed to correlate with both the SCORTEN and the total BSA values. More interestingly, given that the average SCORETEN was 4.3, the predicted mortality rate would have been 58.3%, as per SCORTEN definition; however, in our case series the mortality rate was 8.3% (1 out of 12), significantly lower.

Although our calculations are based on a limited number of patients, we believe these data indicate the efficacy and safety of our therapeutic protocol, in both adults and children.

CsA and plasmapheresis have been individually reported in limited cases as successful second-line therapies for TEN.[3,7–9,15,16] Plasmapheresis has been reported as efficacious in association to methylprednisone and intravenous immunoglobulins in a pediatric case.[15] However, to the best of our knowledge, there are no reported experiences in the literature regarding the association of CsA and plasmapheresis. What's more, there are only 6 reported cases of children with TEN treated with plasmapheresis in the international literature.[3,15,16] Among these, none employs the SCORETEN system to standardize clinical severity and prognosis.

Importantly, our choice to opt for such an uncommon therapy in our cohort came from an elevated SCORETEN value (average 4.3; range 3–7), which reflected in a unified manner the dramatic systemic and cutaneous conditions, thus predicting an unfavorable response to traditional therapies and an elevated mortality rate (58.3%). As a matter of fact we believe that correct standardization, by means of even criteria to classify, evaluate, and manage TEN, can result in better therapeutic guidelines for the care of patients affected by this condition. The decision to employ second- or third-line therapies such as the association of plasmapheresis and intravenous CsA, as effective as they may be, should always be taken on the basis of such rigorous and standardized clinical data. We also believe supportive care in terms of hydroelectrolytic and metabolic equilibration, together with specific topical therapy, do not merely constitute complementary measures, but actively and substantially concur to the clinical improvement.

Surely, further studies on larger cohorts of patients are warranted to confirm the efficacy and safety of our specific therapeutic protocol in TEN, in both adult and pediatric patients.

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PATIENT CONSENT

Patients, parents, or guardians provided written consent for the use of the patients' images.

REFERENCES

1. Heng YK, Lee HY, Roujeau JC. Epidermal necrolysis: 60 years of errors and advances. *Br J Dermatol.* 2015;173:1250–1254.
2. Mockenhaupt M. Stevens-Johnson syndrome and toxic epidermal necrolysis: clinical patterns, diagnostic considerations, etiology, and therapeutic management. *Semin Cutan Med Surg.* 2014;33:10–16.
3. Ferrándiz-Pulido C, Garcîa-Fernández D, Domînguez-Sampedro P, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a review of the experience with paediatric patients in a University Hospital. *J Eur Acad Dermatol Venereol.* 2011;25:1153–1159.
4. Nassif A, Bensussan A, Dorothée G, et al. Drug specific cytotoxic T-cells in the skin lesions of a patient with toxic epidermal necrolysis. *J Invest Dermatol.* 2002;118:728–733.
5. Downey A, Jackson C, Harun N, et al. Toxic epidermal necrolysis: review of pathogenesis and management. *J Am Acad Dermatol.* 2012;66:995–1003.
6. Knowles SR, Shapiro LE, Shear NH. Drug eruptions. In: Schachner LA, Hansen RC, eds. *Pediatric Dermatology.* 3rd ed. London, UK: Mosby; 2003:1267–1276.
7. Fernando SL. The management of toxic epidermal necrolysis. *Australas J Dermatol.* 2012;53:165–171.
8. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part II. Prognosis, sequelae, diagnosis, differential diagnosis, prevention, and treatment. *J Am Acad Dermatol.* 2013;69:187.e1–16.
9. Yamada H, Takamori K. Status of plasmapheresis for the treatment of toxic epidermal necrolysis in Japan. *Ther Apher Dial.* 2008;12:355–359.
10. Paquet P, Piérard GE. Topical treatment options for drug-induced toxic epidermal necrolysis (TEN). *Expert Opin Pharmacother.* 2010;11:2447–2458.
11. Lindford AJ, Kaartinen IS, Virolainen S, et al. Comparison of Suprathel® and allograft skin in the treatment of a severe case of toxic epidermal necrolysis. *Burns.* 2011;37:e67–e72.
12. Abela C, Hartmann CE, De Leo A, et al. Toxic epidermal necrolysis (TEN): the Chelsea and Westminster Hospital wound management algorithm. *J Plast Reconstr Aesthet Surg.* 2014;67:1026–1032.
13. Guégan S, Bastuji-Garin S, Poszepczynska-Guigné E, et al. Performance of the SCORTEN during the first five days of hospitalization to predict the prognosis of epidermal necrolysis. *J Invest Dermatol.* 2006;126:272–276.
14. Beck A, Quirke KP, Gamelli RL, et al. Pediatric toxic epidermal necrolysis: using SCORTEN and predictive models to predict morbidity when a focus on mortality is not enough. *J Burn Care Res.* 2015;36:167–177.
15. Aihara Y, Oyama Y, Ichikawa K, et al. Toxic epidermal necrolysis in a 4-year-old boy successfully treated with plasma exchange in combination with methylprednisolone and i.v. immunoglobulin. *J Dermatol.* 2012;39:951–952.
16. Hinc-Kasprzyk J, Polak-Krzemińska A, Głowacka M, et al. The use of plasmapheresis in a 4-year-old boy with toxic epidermal necrosis. *Anaesthesiol Intensive Ther.* 2015;47:210–213.