Supportive care in the acute phase of Stevens-Johnson syndrome and toxic epidermal necrolysis : an international, multidisciplinary Delphi-based consensus

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Supportive care in the acute phase of Stevens-Johnson syndrome and toxic epidermal necrolysis: an international, multidisciplinary DELPHI-based consensus

Running head: Delphi consensus for supportive care of SJS and TEN

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What's already known about this topic?

- Supportive care is the cornerstone of SJS/TEN management in the acute phase.
- There is no consensus / guidelines on the best supportive care.

What does this study add?

- An international, multidisciplinary consensus on best supportive care practices of SJS/TEN patients in the acute phase.

What are the clinical implications of this work?

- A practical guidance for supportive care of SJS/TEN patients in the acute phase.

Abstract

Background: Supportive care is the cornerstone of adult and pediatric management of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). However, consensus on the modalities of supportive care is lacking.

Objectives: Our aim in this international multicentric Delphi exercise was to establish a multidisciplinary expert consensus to standardize recommendations regarding supportive care in the acute phase of SJS/TEN.

Methods: Participants were sent a survey via the online tool “Survey Monkey” consisting of 103 statements organized into 11 topics: multidisciplinary team composition, suspect drug management, infection prevention, fluid resuscitation and prevention of hypothermia, nutritional support, pain and psychological distress management, management of acute respiratory failure, local skin care, ophthalmological management, management of other mucosa, and additional measures. Participants evaluated the level of appropriateness of each statements on a scale of 1 (extremely inappropriate) to 9 (extremely appropriate). Results were analyzed according to the RAND/UCLA Appropriateness Method.

Results: Forty-five participants from 13 countries (3 continents) participated. After the first round, a consensus was obtained for 84% of the 103 initially proposed statements. After the second round, a final consensus was obtained for 102 statements.

Conclusions: We have reached an international Delphi-based consensus on best supportive care practice for SJS/TEN. Our expert consensus should help guide physicians in treating patients with SJS/TEN and thereby improve short-term prognosis and the risk of sequelae.

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN, or Lyell syndrome) are rare severe delayed-type hypersensitivity reactions, characterized by diffuse epidermal detachment and necrosis. Medications are recognized as the primary trigger factor of the disease, although in 15% of cases no culprit drug can be identified.

The incidence varies among countries and ranges from 1-2 to 6 cases/million inhabitants/year. Mortality in the acute phase is approximately15%. It can be predicted on an individual patient level by applying the SCORTEN (SCORe of Toxic Epidermal Necrolysis). [1–11] SJS and TEN are frequently associated with frequent long-term multiple disabling sequelae that may require prolonged follow-up.[12,13]

SJS and TEN are considered variants on the epidermal necrolysis spectrum. Classification distinguishes them according to body surface area (BSA) involvement. SJS involves skin detachment of less than 10% BSA, SJS/TEN overlap syndrome involves 10–29% BSA, and TEN describes cases of 30% or greater BSA involvement.[14] Associated dermatological manifestations are characterized by dusky macules or atypical targets that can evolve to confluent bullae and skin detachment with a positive Nikolsky's sign.[2,14,15] Mucous membranes are involved in almost all cases.[16–18] The two most frequent complications of SJS and TEN are sepsis,[19] as injured skin can serve as a portal of entry, together with venous/arterial/bladder catheters, and respiratory failure, with the need for mechanic ventilation.[20–23]

The management of SJS/TEN patients in a referral center has been shown to improve patient prognosis.[24–27] To date, there are no standardized recommendations or treatment guidelines for adjuvant treatment in SJS/TEN. Apart from an unsuccessful trial with thalidomide,[28] and a not blinded randomized trial with etanercept versus corticosteroids showing a reduced time to epithelialization with etanercept,[29] there have been no prospective controlled and blinded clinical studies investigating the efficacy of adjuvant, immunomodulatory treatments for SJS/TEN. A variety of different approaches are used in practice, including systemic corticosteroids, intravenous immunoglobulins, cyclosporine, and TNF-antagonists (etanercept).[24,26,30–32] In contrast, there is a published consensus that supportive care is the cornerstone of adult and pediatric SJS/TEN management in the acute phase.[24,26,33] These supportive measures include aspects such as screening and treatment of infectious complications, fluid management and local wound and mucosal care. Although previous studies have shown that improving supportive care may reduce mortality,[6] there is no consensus about best practices related to specific modalities of supportive care treatment. Our aim in this multicenter DELPHI exercise is to harmonize supportive care in the acute phase of SJS/TEN.

Methods

Panel Selection

The project was initiated by the SJS-TEN subgroup (ToxiTEN group) of the skin European Reference Network (ERN-skin), only composed of dermatologists. An international panel of experts in the field of SJS/TEN was established. Participants were identified from academic centers that provide inpatient dermatology or intensive care services specialized in SJS/TEN patient care. In total, 65 experts were identified and invited via email to participate in the Delphi consensus-building exercise. Fifty-five of the identified experts were dermatologists, the additional non-dermatologists were experts in the fields of intensive care/burn unit (4 experts), stomatology (1 expert), ear nose throat (1 expert), ophthalmology (1 expert) and psychiatry (1 expert). In addition, 2 nurses specialized in the care of SJS/TEN were solicited. The non-dermatologists experts were allowed to reply only to the statements they had enough expertise in.

Of the 65 identified experts, 4 did not respond to the invitation to participate, 0 declined, and the remaining 61 agreed to participate.

First Round

In the first round, participants were sent an online survey consisting of 103 statements regarding SJS/TEN. Statements were organized into 11 topic categories, namely: professionals involved, drug management, prevention of infection, fluid resuscitation and prevention of hypothermia, nutritional support, management of pain and psychological distress, management of acute respiratory failure, local skin care, ophthalmological management, management of other mucosa and additional measures. “Survey Monkey”, an online tool, was used to distribute surveys. Participants were asked to evaluate the level of appropriateness of statements on a scale of 1 (extremely inappropriate) to 9 (extremely appropriate). Participants were given the option of selecting “N/A” (not applicable) if they felt they did not have the necessary expertise to rank a particular statement. Participants also had the opportunity to submit comments to be incorporated into subsequent DELPHI rounds. Statements were constructed based on recommendations from existing guidelines on SJS/TEN care.[24,26,33] Additional literature was identified through clinicaltrials.gov and PubMed. Survey results were anonymised prior to releasing them to participants and participants were able to suggest new

statements. Members of the steering committee (MCB, LF, SW, SIHO, SL, and EM) did not respond to the survey**.**

Second Round

During the second round, participants rated the revised statements that failed the previous round and new suggested statements, the work flow is shown in Figure 1.

Statistics

Results were analyzed according to the RAND/UCLA Appropriateness Method. The median rating for appropriateness, interpercentile range (IPR), interpercentile range adjusted for symmetry (IPRAS), and disagreement index (DI) were calculated (DI=IPR/IPRAS) for each statement. [34] Median appropriateness values were assessed as follows: 1.0 to 3.4 was considered "inappropriate", 3.5 to 6.9 as "uncertain" and 7.0 to 9.0 as "appropriate." A disagreement index (DI) greater than or equal to one (≥ 1) indicated a lack of consensus among the participants in terms of a statements' appropriateness.

Results

Participants and Delphi exercise

Forty-five of the 61 participants (coming from 14 countries, 3 continents) who agreed to participate in the DELPHI exercise responded in the first round (74% response rate). In the second round, 41 participants responded (response rate 67%). The statements that the panel "agreed" were "appropriate" and were used to establish a consensus.

First round

A consensus was reached for 85/103 statements (82.5%). All statements and their respective DI and median are displayed in Table S1. Eighteen statements (18/103) had a DI greater or equal to 1 and therefore did not reach the necessary level of agreement (Figure 1). Sections in which participants showed the most disagreement were "Professionals involved in the care of patients with active SJS/TEN" (section I, 10 statements). Consensus lacked for the number of specialists (pneumologist, infectious disease specialist, otolaryngologist, dentist, gynecologist, urologist, psychiatrist, dietician, social worker) that should be involved in SJS/TEN care. Five statements were labelled as uncertain and two as disagreed on in the section "Infection prevention" (section III): these addressed type and frequency of urine analyses and cultures, blood / catheter cultures

and the use of antiseptic baths. Additional uncertain statements were on fluid resuscitation (use of standardized formula), nutritional support (residual gastric volume monitoring) and non-invasive ventilation.

Second round

All of the proposed modified statements passed, with the exception of two statements. The two statements that did not reach consensus were removed from the DELPHI (Table S2). In total, after the two rounds, a consensus was reached for 102 statements (Tables 1-4).

Discussion

The aim of this DELPHI exercise was to establish a multidisciplinary consensus for optimal and standardized acute phase supportive care of SJS/TEN.

Consensus was obtained in key fields of patient management: admission or transfer of the patient in a specialized unit with a medical multidisciplinary team available adapted to the needs of the patient, withdrawal of suspect drug(s), fluid resuscitation, prevention of hypothermia, prevention of infections, topical skin and mucosal care, nutritional support, management of main and psychological distress, management of acute respiratory failure and mechanical ventilation in ICU, and additional measures such as prevention of thrombosis and stress ulceration.

Based on this consensus, we provide a summary of the main key principles of the supportive care to help clinicians in the management of the patient in routine practice (Table 5).

Patients should be admitted or transferred without delay to a specialized unit, within or at close proximity to an intensive care or burn unit, with nurses trained in the management of skin loss. Participants agreed with strong concordance on the involvement of a core team to treat SJS/TEN patients, which should include a dermatologist, pediatrician, intensive care specialist and ophthalmologist. As emphasized in the second DELPHI round, other disciplines (such as gynecologist, psychiatrist, social worker) should only be involved based on the need of that particular patient. No consensus was reached on the involvement of urologists, even when suggested as optional. Although initially included in the DELPHI survey due to potential urethral involvement and strictures, we thereafter

excluded recommending involvement of a urologist.

Given that early discontinuation of the culprit drug is a well-recognized prognostic factor,[35] experts emphasized the need for rapid drug discontinuation, and that identifying the causal medication may be estimated by using the ALDEN score.[8]

Prevention of infection includes hand hygiene, single use non-sterile gloves, a surgical face mask, and daily use of antiseptics. However, a recent French audit of practices showed that aseptic care in burns units is often preferred. However, the impact on the infection risk of sterile versus non-sterile local care and antiseptics in SJS/TEN is unknown.[36] Experts agreed that systemic antibiotics should be prescribed only in documented cases of sepsis, according to the international consensus definition of sepsis and septic shock [37] or in patients with clinical evidence of infection, and guided by susceptibility patterns of bacteria cultured on the patient's skin, urine, blood and/or catheter. Topical antibiotics should be reserved to actively infected areas, for short durations and guided by local microbiology. The use of silver-containing products such as silver sulfadiazine or flammacerium should be very limited (<5% BSA).

Fluid resuscitation, guided by urine output (e.g. 0.5 to 1 mL/kg/h), maintenance of the heating of the room temperature between 25 and 32 °C, and nutritional support, are aimed at compensating the effects resulting from acute skin detachment: fluid, nutrient and electrolyte losses, as well as hypothermia.[38]

In SJS/TEN patients, evaluation and treatment of pain is considered a priority, particularly during wound care and may require high-potency opioids. In recalcitrant cases, pain may warrant transfer to ICU for ketamine infusions or sedation if the intensity of pain prevents local care. Post-traumatic stress is a major long-term complication of SJS/TEN, especially in patients with previous psychological fragility.[39] Regular psychological evaluation is indicated for anticipatory management of this important sequela.

The pathophysiology of SJS/TEN differs from burns namely with healing beginning after 7-10 days. As such, consensus was that the detached epidermis should not be removed. Thus, surgical debridement should only be used if conservative management fails (e.g clinical deterioration, extension of epidermal detachment, local sepsis/sub-epidermal pus, or delayed healing). Several previous studies have also pointed to the need to avoid debridement.[40,41] Due to the lack of convincing efficacy data to date, synthetic skin substitutes or other biological products are not recommended as first-line therapy. White

petrolatum (vaseline) and/or non-adherent dressings are recommended for covering the entire body.

Ophthalmological assessment several times a week is of major importance. Indeed, the severity of ocular involvement during the acute phase is the main risk factor for severe sequelae.[42] The cornerstone of ocular care is the use of lubricant eye drops (without preservatives) and/or vitamin A ophthalmic ointment every 2 hours, with lysis of symblepharons as often as necessary. Topical steroids or antibiotics may be considered in a case-to-case situation, such as amniotic membrane transplantation in the most severe involvements and failure of conservative measures. A recent publication suggested a simple classification of four stages to assess local severity. This publication also included the result of a literature review showing the lack of evidence for topical steroids and antibiotics, encouraging results of amniotic membrane transplantation in the most severe cases, and lack of data concerning symblepharon rings.[43]

Recently, a DELPHI exercise was conducted by the Society of Dermatology Hospitalists on the acute phase care of SJS/TEN patients.[44] Recommendations about general measures, treatment of acute skin failure, wound care and airway management were overall similar to ours. However, our consensus statements regarding pain management and ocular care were different. For the latter, the US group's recommendation for use of topical corticosteroids in the eyes, which has been controversial and lacked consensus per the literature, was not this group's recommendation.[43] Of note, the American dermatologists' DELPHI was not assessed by an international expert panel and combined several messages in contrast to our larger number of more specific recommendations. Methodologically, the median set as threshold for agreement was 6.5 instead of 7, as we performed.

Several limitations need to be considered with regard to our study. The respondents of this DELPHI were multidisciplinary, i.e. from intensive care / burn unit, ophthalmology, stomatology, ear nose throat, pediatrics, psychiatry and dermatology, with the latter representing the majority of the solicited experts. The numeric predominance of dermatologists is due to the fact that this DELPHI was initiated by the ToxiTEN ERN-skin dermatologist expert group and because in European and many other countries,

dermatologists are the cornerstone of SJS/TEN management. The under-representation/lack of certain other specialists, especially burns surgeons, is reflected in our consensus and may have skewed our results. Future studies should aim at soliciting these groups of experts. Also, although many of our statements are applicable to the pediatric setting, it will be worth further specifying children-specific aspects of SJS/TEN care. An additional limitation could be that the respondence rate was slightly lower in the second as compared to the first round of the DELPHI (74% and 67%, respectively).

Conclusion

SJS and TEN are delayed-type hypersensitivity mucocutaneous reactions associated with high morbidity and mortality. To date, the recommended mainstay therapy of SJS/TEN in the acute phase is optimized supportive care, but the specifics of the elements of supportive care that are most important have not been defined in detail with a consensus of experts. Here, through multidisciplinary consensus, we expect our consensus statements to help harmonize SJS/TEN supportive care and guide physicians in treating patients with SJS/TEN thereby improving short-term prognosis and lowering the risk of sequelae.

Contributor statement:

The study was designed by MCB, LF, SW and SIHO. MCB, LF, SW, SIHO, SL, AT and EM elaborated the statements. SL, EM and MCB performed the statistical analyses. All other authors evaluated the statements and contributed to the manuscript.

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References:

1 Kuijper EC, French LE, Tensen CP, *et al.* Clinical and pathogenic aspects of the severe cutaneous adverse reaction epidermal necrolysis (EN). *J Eur Acad Dermatol Venereol* 2020. doi:10.1111/jdv.16339.

2 Duong TA, Valeyrie-Allanore L, Wolkenstein P, Chosidow O. Severe cutaneous adverse reactions to drugs. *Lancet* 2017; **390**:1996–2011.

3 Mockenhaupt M, Viboud C, Dunant A, *et al.* Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. *J Invest Dermatol* 2008; **128**:35–44.

4 Sekula P, Dunant A, Mockenhaupt M, *et al.* Comprehensive survival analysis of a cohort of patients with stevens-johnson syndrome and toxic epidermal necrolysis. *J Invest Dermatol* 2013; **133**:1197–204.

5 Micheletti RG, Chiesa-Fuxench Z, Noe MH, *et al.* Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis: A Multicenter Retrospective Study of 377 Adult Patients from the United States. *J Invest Dermatol* 2018; **138**:2315–21.

6 Bettuzzi T, Penso L, de Prost N, *et al.* Trends in mortality rates for Stevens-Johnson syndrome and toxic epidermal necrolysis: experience of a single centre in France between 1997 and 2017. *Br J Dermatol* 2020; **182**:247–8.

7 Chaby G, Maldini C, Haddad C, *et al.* Incidence of and mortality from epidermal necrolysis (Stevens-Johnson syndrome/toxic epidermal necrolysis) in France during 2003-16: a four-source capture-recapture estimate. *Br J Dermatol* 2020; **182**:618–24.

8 Sassolas B, Haddad C, Mockenhaupt M, *et al.* ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson Syndrome and toxic epidermal necrolysis: comparison with case-control analysis. *Clin Pharmacol Ther* 2010; **88**:60–8.

9 Chaby G, Ingen-Housz-Oro S, De Prost N, *et al.* Idiopathic Stevens-Johnson syndrome and toxic epidermal necrolysis: Prevalence and patients' characteristics. *J Am Acad Dermatol* 2019; **80**:1453–5.

10 Bastuji-Garin S, Fouchard N, Bertocchi M, *et al.* SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol* 2000; **115**:149–53.

11 Hsu DY, Brieva J, Silverberg NB, Silverberg JI. Morbidity and Mortality of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in United States Adults. *J Invest Dermatol* 2016; **136**:1387–97.

12 Ingen-Housz-Oro S, Alves A, Colin A, *et al.* Health-related quality of life and long-term sequelae in survivors of epidermal necrolysis: an observational study of 57 patients. *Br J Dermatol* 2020; **182**:916–26.

13 Lee HY, Walsh SA, Creamer D. Long-term complications of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN): the spectrum of chronic problems in patients who survive an episode of SJS/TEN necessitates multidisciplinary follow-up. *Br J Dermatol* 2017; **177**:924–35.

14 Heng YK, Lee HY, Roujeau J-C. Epidermal necrolysis: 60 years of errors and advances. *Br J Dermatol* 2015; **173**:1250–4.

15 Auquier-Dunant A, Mockenhaupt M, Naldi L, *et al.* Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. *Arch Dermatol* 2002; **138**:1019–24.

16 Bequignon E, Duong TA, Sbidian E, *et al.* Stevens-Johnson syndrome and toxic epidermal necrolysis: ear, nose, and throat description at acute stage and after remission. *JAMA Dermatol* 2015; **151**:302–7.

17 Gueudry J, Roujeau J-C, Binaghi M, *et al.* Risk factors for the development of ocular complications of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Arch Dermatol* 2009; **145**:157–62.

18 Gendreau S, Amiot A, Le Baleur Y, *et al.* Gastrointestinal involvement in Stevens-Johnson syndrome and toxic epidermal necrolysis: a retrospective case series. *Br J Dermatol* 2019; **180**:1234–5.

19 Roujeau JC. Toxic epidermal necrolysis (Lyell syndrome): more than 'acute skin failure'. *Intensive Care Med* 1992; **18**:4–5.

20 Lecadet A, Woerther P-L, Hua C, *et al.* Incidence of bloodstream infections and predictive value of qualitative and quantitative skin cultures of patients with overlap syndrome or toxic epidermal necrolysis: A retrospective observational cohort study of 98 cases. *J Am Acad Dermatol* 2019; **81**:342–7.

21 Koh HK, Chai ZT, Tay HW, *et al.* Risk factors and diagnostic markers of bacteremia in Stevens-Johnson syndrome and toxic epidermal necrolysis: A cohort study of 176 patients. *J Am Acad Dermatol* 2019; **81**:686–93.

22 de Prost N, Mekontso-Dessap A, Valeyrie-Allanore L, *et al.* Acute respiratory failure in patients with toxic epidermal necrolysis: clinical features and factors associated with mechanical ventilation. *Crit Care Med* 2014; **42**:118–28.

23 Lebargy F, Wolkenstein P, Gisselbrecht M, *et al.* Pulmonary complications in toxic epidermal necrolysis: a prospective clinical study. *Intensive Care Med* 1997; **23**:1237–44.

24 Ingen-Housz-Oro S, Duong T-A, Bensaid B, *et al.* Epidermal necrolysis French national diagnosis and care protocol (PNDS; protocole national de diagnostic et de soins). *Orphanet J Rare Dis* 2018; **13**:56.

25 Kaffenberger BH, Rosenbach M. Toxic epidermal necrolysis and early transfer to a regional burn unit: Is it time to reevaluate what we teach? *J Am Acad Dermatol* 2014; **71**:195–6.

26 Creamer D, Walsh SA, Dziewulski P, *et al.* U.K. guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016. *Br J Dermatol* 2016; **174**:1194–227.

27 Traikia C, Hua C, Le Cleach L, *et al.* Individual- and hospital-level factors associated with epidermal necrolysis mortality: a nationwide multilevel study, France, 2012-2016. *Br J Dermatol* 2020; **182**:900–6.

28 Wolkenstein P, Latarjet J, Roujeau JC, *et al.* Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. *Lancet* 1998; **352**:1586–9.

29 Wang C-W, Yang L-Y, Chen C-B, *et al.* Randomized, controlled trial of TNF-α antagonist in CTL-mediated severe cutaneous adverse reactions. *J Clin Invest* 2018; **128**:985–96.

30 Ingen-Housz-Oro S, Duong T-A, de Prost N, *et al.* [Treatment of severe cutaneous adverse drug reactions]. *Ann Dermatol Venereol* 2018; **145**:454–64.

31 White KD, Abe R, Ardern-Jones M, *et al.* SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation. *J Allergy Clin Immunol Pract* 2018; **6**:38–69.

32 Zimmermann S, Sekula P, Venhoff M, *et al.* Systemic Immunomodulating Therapies for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Systematic Review and Meta-analysis. *JAMA Dermatol* 2017; **153**:514–22.

33 McPherson T, Exton LS, Biswas S, *et al.* British Association of Dermatologists' guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in children and young people, 2018. *Br J Dermatol* 2019; **181**:37–54.

34 Jandhyala R. Delphi, non-RAND modified Delphi, RAND/UCLA appropriateness method and a novel group awareness and consensus methodology for consensus measurement: a systematic literature review. *Curr Med Res Opin* 2020; **36**:1873–87.

35 Garcia-Doval I, LeCleach L, Bocquet H, *et al.* Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol* 2000; **136**:323–7.

36 Ingen-Housz-Oro S, Le Floch R, Alves A, *et al.* Carrying out local care for epidermal necrolysis: survey of practices. *J Eur Acad Dermatol Venereol* 2020. doi:10.1111/jdv.16884.

37 Singer M, Deutschman CS, Seymour CW, *et al.* The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**:801–10.

38 Inamadar AC, Palit A. Acute skin failure: concept, causes, consequences and care. *Indian Journal of Dermatology, Venereology and Leprology* 2005; **71**:379–85.

39 Hefez L, Zaghbib K, Sbidian E, *et al.* Post-traumatic stress disorder in Stevens-Johnson syndrome and toxic epidermal necrolysis: prevalence and risk factors. A prospective study of 31 patients. *Br J Dermatol* 2019; **180**:1206–13.

40 Castillo B, Vera N, Ortega-Loayza AG, Seminario-Vidal L. Reply to: 'Wound management strategies in Stevens-Johnson syndrome/toxic epidermal necrolysis: An unmet need'. *J Am Acad Dermatol* 2018; **79**:e89.

41 Lee HY. Wound management strategies in Stevens-Johnson syndrome/toxic epidermal necrolysis: An unmet need. *Journal of the American Academy of Dermatology* 2018; **79**:e87–8.

42 Hajj C, Ezzedine K, Thorel D, *et al.* Disabling ocular sequelae of epidermal necrolysis: risk factors during the acute phase and associated sequelae. *Br J Dermatol* 2019; **181**:421–2.

43 Thorel D, Ingen-Housz-Oro S, Royer G, *et al.* Management of ocular involvement in the acute phase of Stevens-Johnson syndrome and toxic epidermal necrolysis: french national audit of practices, literature review, and consensus agreement. *Orphanet Journal of Rare Diseases* 2020; **15**:259.

44 Seminario-Vidal L, Kroshinsky D, Malachowski SJ, *et al.* Society of Dermatology Hospitalists supportive care guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults. *Journal of the American Academy of Dermatology* 2020; **82**:1553–67.

Table 1. Statements that the panel agreed were appropriate for professionals involved and drug management in active SJS/TEN patients

Item	Disagreement index*
I. Professionals involved in the care of patients with active SJS/TEN	
Patients should be admitted or transferred to a specialty service (e.g. dermatology, intensive care unit, burn surgery unit).	**0.00**
Specialty units (e.g. dermatology, intensive care unit, burn unit) should be notified immediately upon admission of patients.	**0.01**
Patients should be managed by a multidisciplinary team lead by either dermatology, burn surgery, or an intensive care.	**0.03**
A dermatologist should be involved in the management of SJS/TEN.	**0.01**
An intensive care specialist should be involved in the management of SJS/TEN.	**0.20**
A pediatrician (if child affected) should be involved in the management of SJS/TEN.	**0.30**
An ophthalmologist should be involved in the management of SJS/TEN.	**0.02**
A specialized nurse (e.g. burn nurse) should be involved in the management of SJS/TEN.	**0.10**
A pulmonologist is sometimes helpful in the management of SJS/TEN.	**0.49**
An infectious disease specialist is sometimes helpful in the management of SJS/TEN.	**0.29**
An otolaryngologist is sometimes helpful in the management of SJS/TEN.	**0.49**
A specialized dentist (e.g. stomatologist) is sometimes helpful in the management of SJS/TEN.	**0.82**
A gynecologist (if female affected) is sometimes helpful in the management of SJS/TEN.	**0.45**
A gastroenterologist is sometimes helpful in the management of SJS/TEN.	**0.65**
A psychiatrist (or psychologist) is sometimes helpful in the management of SJS/TEN.	**0.29**
A dietician is sometimes helpful in the management of SJS/TEN.	**0.38**
A social worker is sometimes helpful in the management of SJS/TEN.	**0.38**
II. Drug Management in patients with active SJS/TEN	
Suspected drugs should be immediately discontinued.	**0.00**
Unsuspected essential drugs should not be discontinued, even if they have known associations with SJS/TEN.	**0.38**
The ALDEN (or similar score) is helpful in assessing drug causality.	**0.25**

The ALDEN (or similar score) should be calculated for every drug suspected.	**0.33**
A center for drug evaluation (i.e. pharmacovigilance center) should be contacted if drug causality is unclear.	**0.84**

**A disagreement index value below 1 indicated a consensus among the participants*

Table 2. Statements that the panel agreed were appropriate for infection prevention, fluid resuscitation and nutritional support.

Item	Disagreement index*
III. Infection Prevention for SJS/TEN patients with active disease	
Hand hygiene, single use non-sterile gloves, and a surgical face mask should always be used.	**0.07**
Strict standard operating procedures should be followed for invasive procedures such as central catheter placement.	**0.00**
Prophylactic systemic antibiotics are not recommended without indication.	**0.05**
Systemic antibiotics should only be administered in cases of sepsis or invasive infection or in patients with vital signs or laboratory findings (e.g. positive blood cultures) or clinical presentation consistent with infection.	**0.01**
Routine skin cultures should occur to investigate and follow bacterial skin colonization every 2-3 days, especially on sloughy or crusted areas.	**0.65**
Topical antimicrobial agents should not be routinely used due to risk of allergy and microbial resistance.	**0.88**
If used, topical antimicrobial agents (e.g. fusidic acid or silver sulfadiazine) should only be applied for short durations in the treatment of actively infected areas.	**0.24**
Choice of topical antimicrobial agents should be guided by knowledge of local microbiology.	**0.23**
Choice of antimicrobial agents should be guided by susceptibility patterns of bacteria cultured on the patient's skin, urine, blood and/or catheter.	**0.02**
Silver containing products (e.g. silver sulfadiazine or flammacerium) should not be used in patients with sulphonamide-triggered SJS/TEN.	**0.89**
If used, silver-containing products should be limited to 5% or less of BSA due to risk of absorption.	**0.89**
Peripheral (or central if no peripheral access) catheters should be used inserted into unbroken skin when possible.	**0.02**
Central catheters containing antimicrobial agents (e.g. silver sulfadiazine or chlorhexidine) may be considered except if contraindicated.	**0.35**
Eroded or vesicular skin, particularly in the genital or oral distribution, should be investigated for herpes simplex virus.	**0.19**
Routine blood cultures should be obtained at baseline.	**0.89**
Routine blood cultures should occur regularly, especially in cases of any	**0.49**

clinical suspicion of sepsis.	
Routine urine analysis (e.g. dipstick) should be obtained at baseline.	**0.38**
Routine urine analysis (e.g. dipstick) should occur regularly, especially in cases of any clinical suspicion of sepsis.	**0.66**
Routine IV catheter culture should occur when changing the device.	**0.49**
Application of antiseptic agents (e.g. diluted aqueous chlorhexidine) should be used daily.	**0.63**
IV. Fluid Resuscitation and Prevention of Hypothermia in patients with active SJS/TEN	
Fluid resuscitation should be adapted on a case-by-case basis.	**0.03**
Fluid resuscitation should be less aggressive than for burn patients to avoid pulmonary, cutaneous or intestinal oedema.	**0.36**
Hemodynamic status should be monitored every two to four hours.	**0.24**
Fluid volume should be tailored to urine output (e.g. 0.5 to 1 mL/kg/h).	**0.18**
Development of hypothermia should be actively monitored and prevented.	**0.01**
Room temperature should be kept between 25 and 32°C.	**0.16**
Warmed inspired gases, warmed or room-temperature fluids, and warming blankets should be used if necessary.	**0.08**
A standardized formula (e.g modified Brooke formula or Parkland formula) may be used to guide initial fluid resuscitation.	**0.16**
V. Nutritional support for patients with active SJS/TEN	
Early nutritional support by continuous enteral nutrition should be used.	**0.26**
The nutritional target is 20 kcal/kg/day, to be slowly increased to 30 kcal/kg/day.	**0.30**
Enteral nutrition should be avoided in patients with extensive oesophageal involvement.	**0.83**
Parenteral nutrition should be used in patients with oesophageal involvement.	**0.29**
Blood glucose levels should be monitored at least once a day.	**0.19**
Insulin treatment should be initiated if two consecutive blood glucose readings exceed 180 mg/dL, with a target glucose of less than or equal to 180 mg/dL.	**0.37**

**A disagreement index value below 1 indicated a consensus among the participants*

Table 3. Statements that the panel agreed were appropriate for psychological distress, acute respiratory failure and ophthalmological management.

Item	Disagreement index*
VI. Pain and psychological distress management for patients with active SJS/TEN	
Pain and the efficacy of pain medications should be regularly assessed and documented.	**0.00**
Evaluation and treatment of pain should be a priority in the acute phase management of SJS/TEN, particularly during wound care.	**0.01**
The efficacy of pain medications should be assessed with a visual analogue scale according the age of the patient.	**0.05**
Opioids should be used in most cases of SJS/TEN.	**0.28**
High-potency opioids (e.g. morphine) should be used if the VAS score is elevated.	**0.27**
Non-oral formulations of opioids (e.g. intra-nasal diamorphine or sublingual fentanyl) may be used for limited procedures, unless active disease in these distributions precludes use.	**0.38**
Non-opioid agents (e.g. ketamine infusions) may be used over opioids during wound care in the ICU.	**0.29**
Sedation and mechanical ventilation may be used to achieve pain control.	**0.17**
Psychiatric and/or psychological evaluation should be effected to reduce post-traumatic stress disorder.	**0.10**
VII. Management of acute respiratory failure in patients with active SJS/TEN	
Patients should be monitored closely in case of respiratory decompensation.	**0.00**
Patients should be transferred to the ICU in case of respiratory decompensation.	**0.00**
Chest x-ray and arterial blood gases should be obtained upon admission to assess respiratory status.	**0.06**
Active disease in the tracheobronchus should be suspected in the presence of respiratory signs or symptoms (e.g. productive cough, dyspnea, hypoxemia) or consistent radiological findings.	**0.03**
Bronchoscopy may be considered for diagnostic and therapeutic purposes.	**0.27**
Endotracheal intubation and mechanical ventilation should be used in the presence of impaired consciousness, hemodynamic instability, or acute respiratory distress.	**0.00**
If needed, invasive ventilation should be preferred to non-invasive ventilation given the risk of upper airway obstruction.	**0.16**

VIII. Local skin care for patients with active SJS/TEN	
Pressure should be limited on affected skin by use of appropriate beds.	**0.00**
Detached epidermis should not be removed in patients with SJS/TEN.	**0.22**
Surgical debridement should only be used if conservative management fails (e.g clinical deterioration, extension of epidermal detachment, local sepsis/sub-epidermal pus, or delayed healing).	**0.17**
Tense bullae should be pierced and aspirated, allowing the blister roof to settle onto the underlying dermis.	**0.10**
The entire skin surface may be covered with non-adherent dressings or white petroleum.	**0.13**
The denuded skin surface should be covered with non-adherent dressings.	**0.07**
Synthetic skin substitutes or other biological products (Human Placenta-Derived Extracellular Matrix Containing Bioactive Molecules/Cryopreserved placental membrane) may be considered but there is insufficient evidence on their efficacy in early wound coverage.	**0.26**
Catheters should be secured with non-adhesive dressings.	**0.13**
IX. Ophthalmological surveillance in patients with active SJS/TEN	
Ophthalmologic evaluation should occur within 24 hours of presentation.	**0.00**
Follow up ophthalmologic evaluation should occur at least twice a week until discharge.	**0.01**
Power score (e.g. mild, moderate, severe) or simplified grading (e.g. no involvement, mild, severe or very severe) should be used to evaluate the severity of eye involvement.	**0.07**
Local eye care (e.g. lubricant eye drops without preservatives and/or vitamin A ophthalmic ointment) should be administered every 2 hours.	**0.06**
Anti-microbial eye drops without preservatives may be used if necessary.	**0.10**
Broad-spectrum topical antibiotic prophylaxis may be recommended in the presence of deficits on corneal fluorescein staining or frank ulceration (when microbial keratitis has been excluded).	**0.33**
Symblepharon lysis should be performed as often as necessary by an ophthalmologist.	**0.02**
Topical corticosteroids may be considered.	**0.18**
The use of topical corticosteroid therapy is debated.	**0.64**
Amniotic membrane transplantation and plastic symblepharon rings MAY be considered if conservative measures fail.	**0.12**

Table 4. Statements that the panel agreed were appropriate for mucosal surveillance and additional measures of SJS/TEN care.

Item	Disagreement index*
X. Surveillance of other mucosae in patients with active SJS/TEN	
Mucosal lesions should be evaluated thoroughly.	**0.00**
Accessible sites (including the outer ear) should be evaluated daily.	**0.02**
The oropharyngeal and gynecological distribution of mucosa should be examined at admission and at least once weekly until discharge.	**0.03**
Anti-microbial and analgesic mouthwashes should be used several times daily.	**0.11**
Paraffin-based ointments should be frequently applied to the lips (e.g. every 2 hours).	**0.13**
Paraffin-based ointments should be applied on the glans in men and the vagina in women.	**0.13**
Daily foreskin mobilization should be performed in men.	**0.13**
XI. Additional measures in patients with active SJS/TEN	
Upper gastrointestinal stress ulcer prophylaxis should be used in patients without enteral nutrition.	**0.13**
Proton pump inhibitors should be used for ulcer prophylaxis except when suspected as trigger.	**0.13**
Prophylactic anticoagulation (e.g. low molecular weight heparin) should be used unless contraindicated.	**0.68**
Blood pressure, heart rate, temperature, respiratory rate and oxygen saturation should be monitored every 2 to 4 hours.	**0.15**
Routine weight monitoring should be performed every 2 to 3 days until discharge.	**0.26**

Table 5. Supportive care of SJS and TEN.

Measures	Commentaries
General measures	
Transfer in specialized multidisciplinary setting	Dermatology department, intensive care unit (ICU), burn unit *Always notify specialty service upon admission Additional specialities may be consulted depending on severity and involvement
Drug management	Immediate discontinuation of culprit drug(s) ALDEN score may help for causality determination
Temperature of the room	Ambient temperature between 25 and 32°C
Management of pain	Regular assessment of pain using visual analogue scale Opioids (morphine, fentanyl), non-opioids (ketamine, only in ICU)
Prevention of psychological distress	According psychiatric and/or psychological evaluation
Hydration	Fluid resuscitation adapted on a case by case basis Standardized formula may guide initial fluid resuscitation Fluid intake adapted according to hemodynamic status and urine output (e.g. 0.5 to 1 ml/kg/h) monitored every 2 to 4 hours
Nutritional support	Continuous enteral nutrition except if oesophageal involvement Parenteral nutrition if oesophageal involvement Target 20 to 30 kcal/kg/day of exact body weight Daily monitoring of blood glucose and treat with insulin if > 180 mg/dL
Prophylaxis of thromboembolism	Thromboprophylaxis unless contraindication
Prevention of infections	Hand hygiene, single use non-sterile gloves, surgical face mask Regular skin swabs or skin cultures until healing Regular bedside dipstick urinalysis (nitrites, leucocytes and glucose) Regular blood culture, especially if signs of sepsis Systemic antibiotics only if documented sepsis or strong clinical/biological signs of invasive infection
Local care	

Antiseptic measures	Antiseptics daily (e.g. diluted aqueous chlorhexidine) No topical antibiotics except if needed and according results of local microbiology on actively infected areas No silver sulfadiazine except if needed, i.e. in actively infected areas
Skin care	Pierce blisters but no removal of the detached epidermis Surgical debridement only if failure of conservative treatment Cover the entire skin, including denuded skin, with non-adherent dressings or white petroleum
Ocular care	Lubricant eye drops without preservatives and/or vitamin A ophthalmic ointment every 2 hours Removal of symblepharons If needed, according ophthalmologist's opinion: -Topical steroids and antibiotics -Amniotic membrane transplantation and plastic symblepharon rings
Genital care	Paraffin-based ointments Men: daily foreskin mobilization
Oral care	Anti-microbial and analgesic mouthwashes several times daily Paraffin-based ointments on the lips

Figure Legends

Figure 1. Flowchart illustrating the work steps of the DELPHI exercise.

Figure 1

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