A SYSTEMATIC REVIEW OF TREATMENT OF DRUG-INDUCED STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS IN CHILDREN

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ABSTRACT

Stevens-Johnson (SJS) and Toxic Epidermal Necrolysis (TEN) are two uncommon mucocutaneous diseases usually considered as severe drug reactions and are characterized by different grades of epidermal necrosis. Several treatment modalities have been proposed with variable results but the lack of controlled studies makes difficult to analyze them objectively especially in children. All publications describing management for SJS and TEN in children were searched in MEDLINE, EMBASE, and the Cochrane Library. Reports included were divided in two categories: A, studies with 5 or more patients and observational studies; and B, reports with less than 5 patients. A formal meta-analysis was not feasible. Description was made using central tendency measures. From 1389 references only 31 references with a total of 128 cases were included, 88 category A and 40 category B. The 4 main treatment modalities were: intravenous immunoglobulin (IVIG), steroids (prednisolone, methylprednisolone, dexamethasone), dressings with or without surgical debridement, and support treatment alone. Miscellaneous treatments: Of 12 patients, 3 received ulinastatin, 4 patients plasmapheresis, 2 patients IV pentoxifylline and the last three patients received different treatment each (cyclosporine, methylprednisone/G-CSF and methylprednisolone/IVIG). Patients receiving IVIG and steroids showed similar findings while patients treated with dressing and support treatment alone, reported both longer time to achieve remission and hospitalization stays and appear to be associated with more complications and deaths. There is scant quality literature about management of SJS and TEN in children. Steroids and IVIG seem to improve the outcome of SJS and TEN patients but results from different reports are variable. Patients treated only with care support seem to have higher morbidity and mortality. Further studies are necessary to define optimal management.

Key Words: Stevens-Johnson syndrome; toxic epidermal necrolysis; children; drugs; systematic review

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tevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are two mucocutaneous diseases associated with significant morbidity and mortality. They are characterized by skin tenderness and erythema of skin and mucosa, followed by extensive cutaneous and mucosal epidermal necrosis and sloughing. The precise incidence of SJS and TEN in children is unknown. Although some work has been carried out on the epidemiology of these two entities, most studies have been made in the general population and some were before the development of the current classification system, thus some cases of EM and other misdiagnosed dermatoses were included.¹ A German study calculated an overall annual risk in the general population of 0.93 and 1.1 per million for TEN and SJS, respectively.² Other authors have estimated 0.4 to 1.2 per million for TEN and 1.2 to 6 per million for SJS.³,⁴ Clinical characteristics
of SJS differ from those of TEN and a third condition named SJS/TEN overlap which usually shows combinations of both. Patients may present with a clinical picture of SJS that evolves to one of toxic epidermal necrosis within a few days. The child with SJS looks acutely ill, febrile, and often has a prodrome of an upper respiratory illness. Hemorrhagic crusts can develop on the lips and mucous membranes are severely affected. This may be associated with burning pain. The skin eruption consists of symmetrical red maculae which progress to central blister formation. These lesions are distributed on the face and upper trunk, areas that usually remain the most severely affected. The rash spreads centrifugally, sometimes within hours. Lymphadenopathy is frequently present and enlargement of the liver and spleen may be present. Skin biopsy shows extensive epidermal necrosis with paucity of inflammatory cells. Conversely, 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 children, an acute sunburn-like appearance with evolution into extensive epidermal necrosis is seen.

Frequently skin denudes when the child is handled (Nikolski’s sign). Skin biopsy of TEN shows that the level of epidermal separation is sub-epidermal and it is accompanied with overlying epidermal necrosis. In both cases the re-growth of epidermis may begin, if there is no skin infection, within days but usually takes about three weeks.

SJS and TEN are considered severe cutaneous drug reactions, but there is some evidence that other agents such as *M. pneumonia*, vaccines, and some neoplastic and autoimmune diseases may play a role in their etiology. Less than 5% of the patients cannot be related to any aetiology, while an association of SJS and TEN with drugs is found in 77 to 95 percent of patients. Although the relative proportion depend on the source, antibacterial and anticonvulsants are more frequently referred as causing SJS and TEN, followed by analgesics, non steroid anti-inflammatory drugs and corticosteroids. Currently more than 100 drugs have been associated with SJS and TEN.

Recently, Bastuji-Garin conducted a prospective case-control study to standardize and classify clinical characteristics of Erythema Multiforme, SJS and TEN. This new classification proposed five categories as shown in Table 1.

**TABLE 1 Classification of acute severe bullous disorders**

<table>
<thead>
<tr>
<th></th>
<th>Bullous EM</th>
<th>SJS</th>
<th>Overlap</th>
<th>TEN With</th>
<th>TEN without</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>SJS/TEN</td>
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<td>Detachment % BSA</td>
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</tr>
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</table>

EM Erythema Multiforme; SJS Stevens-Johnson Syndrome, TEN Toxic Epidermal Necrolysis; BSA Body Surface Area
Currently this classification is used in almost all textbooks and studies about SJS and TEN. Even though the Bastuji-Garin classification helps to clinically classify EM, SJS and TEN, there are still different opinions on whether EM major and SJS are or not the same disease as well as their relationship with causal agents. Unfortunately, this classification does not provide clear differences between infectious or drug etiology. Forman in 2002 decided to validate Bastuji-Garin’s classification in pediatric population. She undertook a retrospective analysis of 61 cases of SJS, Bullous EM and TEN from a 10 years period in a tertiary care pediatric hospital and applied the new classification. The study also reviewed important information such as gender, age, past medical history and antecedent use of medications. The results showed that after reassigning the diagnosis, patients with EM were related in 82% of cases with infectious etiology, most of them herpes simplex virus, and only 18% with drugs; additionally, patients with SJS were related in 91% with drugs and only in 4.5% with an infectious etiology. Overlap and TEN cases were all attributed to drugs only. More recently, Roujeau has suggested separating definitively EM major as a different entity, from the SJS/TEN group and reassigned new names to SJS, SJS/TEN overlap, and TEN as Ruiz-Maldonado had previously suggested.

The relevance of SJS and TEN for many authors does not relate to its occurrence, because fortunately these entities are uncommon. However, the high morbidity, incapacitating sequelae and associated mortality represent a high emotional and economical cost. The morbidity results not only from the extensive denuded skin areas, but it also depends on the visceral involvement particularly in the gastrointestinal and respiratory systems. The involvement of the larynx and tracheobronchial tree is commonly associated with airway compromise and progressive respiratory failure. Gastrointestinal involvement could be seen in all areas with both obstruction and perforation complications. One of the most important complications because of its devastating sequelae is the ocular involvement that may include bacterial conjunctivitis, suppurative keratitis, and endophthalmitis. Late complications include impaired tear production and drainage, aberrant lashes, metaplasia of the conjunctiva, and corneal ulcers. In addition to skin infections, which are associated with high mortality, skin sequelae include scarring, dyschromia (hypo-hyperpigmentation), eruptive nevomelanocytic nevi and nail deformities.

Previously, SJS and TEN were associated with a mortality ranging from 25% to 70%, usually resulting from sepsis or organ failure but fortunately, improvements in supportive care systems and early referral to burn units has decreased mortality to 5% to 30%, albeit with patients with TEN generally reported to have higher mortality.

One of the problems associated with reducing the morbidity and mortality in SJS and TEN patients is the underestimation of the severity of these entities, as occasionally the systemic condition of the patients does not correlate with the skin affection. Some patients show clinical characteristics of SJS and rapidly evolve to severe TEN. Currently physicians have useful tools that help them to evaluate the initial condition and progression of patients with SJS and TEN. One is SCORTEN, a SJS/TEN-specific severity-of-illness score based on a minimal set of well-defined variables evaluated during the 24 hours after patient admission to hospital and during hospitalization. It evaluates seven predictive factors, namely age ≥ 40 years, presence of malignancy, detached body surface area ≥ 10%, tachycardia ≥ 120/min, serum urea >10mmol/L, serum glucose >14mmol/L, and serum bicarbonate <20mmol/L with each of these factors having a value of one point. The SCORTEN has been well validated and has been used by several investigators, but in pediatric literature is scarcely referred. In 2006, Guegan et al. found SCORTEN useful to predict disease outcome in TEN patients, and although SCORTEN might vary during hospitalization its performance is excellent, with a predictive value at its best on day 3. Although this score has not been specifically validated in children (in spite of having been derived from a cohort including both children and adults) it has been suggested that the prognosis of SJS and TEN in children is better than in adults and it is associated with lower mortality and faster re-epithelization.

The development of new treatments for SJS and TEN patients has been driven by pathology, but it remains controversial as results obtained by...
different authors are often contradictory and controlled studies are lacking. Although many authors agree that early diagnosis, withdrawal of all potentially responsible agents and adequate support treatment have to be prompt until now there is no standard treatment for children with these entities. The mainstay of management is admission to a burn unit or a pediatric intensive care unit. An accurate assessment of the affected BSA is necessary to determine hospitalization requirements, volume of fluid resuscitation, nutritional requirements and prognosis. The classic “rule of 9s” may lead to significant errors in estimation in children; therefore, it is more practical to use the area of a child’s palm that represents approximately 1% of TBSA. The essential management also includes establishment of permeable airway, correction of fluid and electrolyte imbalance, pulmonary toilet, caloric replacement, protection from secondary infections and meticulous ophthalmologic care. Some authors refer that in areas where the affected skin is not detached antimicrobial ointments are not needed as the skin’s integrity has not been violated while some studies consider that large blisters or those that have ruptured should be surgical debrided and an antimicrobial ointment and/or biological dressings applied. Since an immunologic process is possibly involved in SJS and TEN numerous studies have focused in the use of drugs that modify the immunologic response including corticosteroids, intravenous immunoglobulin (IVIG), cyclophosphamide, N-Acetylcystine, Granulocyte colony stimulating factor, heparin, monoclonal antibodies and thalidomide. However, many of the reports on these therapies are uncontrolled studies, anecdotal cases and have included few or no children at all. Two major school divide physicians: steroids vs. IVIG. In the last few years, new studies have been trying to demonstrate the efficacy of steroids and IVIG as ideal treatment for SJS and TEN, but still there is not enough and accurate evidence supporting that these treatments really improve the outcome of SJS and TEN patients.

Even though a number of reviews of the treatment of SJS and TEN in children have been published; to the best of our knowledge none of them has been conducted in a systemic manner, therefore the principal objective of this work was to systematically evaluate all the available evidence regarding the treatment of SJS and TEN in children.

METHODS

The search focused on all publications describing or potentially describing a study that proposes or reviews treatments or interventions that improve the evolution of pediatric patients with diagnosis of SJS and TEN using the search strategy shown in the Appendix. The search included the following electronic databases: MEDLINE, EMBASE, and the Cochrane Library (Including: The Cochrane Database of Systematic Reviews, the Database of abstracts of Reviews of effects, The Cochrane Controlled Trials Register and The Health Technology Assessment Databases). No language or date restrictions were considered. The retrieved references were assessed for possible inclusion on the basis of the evaluation of the title and the abstract, or in full if no abstract was available. Letters to the editor, review articles, editorials and commentaries were excluded.

Criteria for Considering Articles for Review

We specifically aimed to retrieve randomized controlled trials, in the absence of which we decided to further include cohort studies, case-control studies, and case series – case reports. The studies had to propose any therapeutic or surgery intervention used to treat pediatric patients (0-18 year old) with established diagnosis of SJS and TEN by clinical criteria and/or skin biopsy.

Methods of the Review

The quality of the observational studies was assessed according to the STROBE statement. Reports were divided in two categories: in category A we included observational studies and case series with 5 or more patients. Category B was conformed by case reports of one to four patients or by pediatric patients taken from larger series that included also adults. Initially we aimed to use mortality and severe sequelae as main outcome measures; however, due to the lack of information availability we limited the report to the secondary outcomes, namely time to achieve objective response, time to remission and length of hospital stay.
Statistical Analysis
A formal meta-analysis was not conducted due to the heterogeneity among the publications. Data was extracted and summarized using central tendency measures, using ranges, and medians or means, as provided by the authors. Because this sample might not have a normal distribution, no attempt was made to approximate confidence limits for the proportions.

RESULTS

Literature Search Results
The search yielded 1389 references, of which 1350 were excluded. We were unable to retrieve 8 case reports; 31 references were fully evaluated and included in the final analysis.

Characteristics of Included Studies and Methodological Quality
Table 2 shows the design of the included references. We found 1 pseudo-randomized prospective study, 12 cohort studies (6 prospective, 6 retrospective), and 18 case reports and case series. Four of the cohort studies included both adults and children. The cohort studies adhered poorly to the STROBE statement recommendations.

Patients’ Characteristics and Treatment Response
The total number of patients included in reports from both categories was 128; eighty-eight patients included in reports from category A and forty patients in reports from category B. In all patients drugs and *Mycoplasma pneumoniae* were the most common etiologies, but viral infections and unknown agents were also reported. We grouped the patients depending on the main treatment received; demographics and outcomes are described separately for each group. The main demographic information and outcomes data are shown in Table 3.

Four main treatment modalities were used: intravenous immunoglobulin (IVIG), steroids (prednisolone, methylprednisolone, dexamethasone), dressings with or without surgical debridement, and supportive treatment alone. In addition several other therapies were also used in case reports or smalls series including cyclophosphamide, cyclosporine, pentoxifylline, plasmapheresis, and ulinastatin.

Patients treated with intravenous immunoglobulin
The group of patients treated with IVIG consisted of 57 patients with age ranging between 0.4 and 15 years. Some patients received one or two doses of steroids prior to their hospital admission and IVIG. TEN was the most frequent diagnosis with 33 patients followed by SJS with 18 patients and 6 patients with SJS/TEN overlap. The doses received ranged from 0.25 to 1.5 g/kg/d for one to five days. Time from diagnosis to treatment initiation days was 1 to 10 days. Time to objective response (defined on the reports as lack of fever after treatment onset) ranged from 1 to 3 days. Time to achieve remission since diagnosis was between 4 and 18 days. Hospital stay (available in 11 out of 23 reports) was reported with a range from seven to forty two days. Complications were systematically informed only in 1 case series consisting on mild infections. In the remaining reports there were one patient with sepsis, two treatment failures, one case of rhabdomyolysis, one severe bleeding and one severe neutropenia. No deaths were reported.

Patients treated with steroids
The second group including patients treated with steroids included 20 patients and the age range was from 6 to 15 years. Five patients (25%) were females and 15 (75%) were males. Nineteen patients had a diagnosis of SJS and only one had SJS/TEN overlap. No time from diagnosis to treatment was reported. Patients received either prednisolone or prednisone (1 mg/kg/d) or methylprednisolone (4 mg/kg/d) during 5 to 7 days. Time to objective response was reported in 14 patients ranging from 1 to 4 days, while time to achieve remission since diagnosis was available in only 16 patients and it was 7 to 16 days. Only two patients reported hospital stays of 12 and 30 days. Complications were observed in 5 patients, 3 mild skin infections and 2 cases of bronchiolitis obliterans. There were no deaths in this group.

Patients treated with dressings
The third group included 1 case series of ten patients and 3 case reports that were treated with dressings (Acticoat™, Biobrane™ and silver nitrate) with or without surgical debridement, along with supportive treatment. All of these patients had a diagnosis of Toxic epidermal Necrolysis with an affected BSA between 50 and
95 percent. No time of diagnosis to treatment was referred. Time to objective response was reported in 2 patients as 3 and 7 days. Time to achieve remission since diagnosis was reported in only 3 patients between 10 to 12 days and the hospital stay in all patients was from twelve to thirty five days. Nine out of ten patients from the case series presented complications such as sepsis but none of thirteen patients died.

**Patients treated with supportive care**

The fourth group consisted of 3 case series and 3 case reports with supportive treatment as only management. This group included 33 patients age 2 - 17 years. Sixteen patients (48.5%) were males and seventeen (51.5%) were females. Stevens Johnson Syndrome was the diagnoses in 27 patients, 3 patients had TEN (no affected BSA was reported) and 3 had SJS/TEN overlap with 21% BSA. Supportive treatment was initiated after admission and it consisted of an intensive care unit management of electrolyte and energy intake, pain control and sedation, antibiotics if there was evidence of any infection and dermatological care of affected skin. Only 1 case series and 2 case reports reported time to objective response which ranged between 3 and 9 days. No hospital stay was stated. Time to achieve remission since diagnosis ranged from 7 to 22 day. Information about the hospital stay was available in only one patient and it was six days. Six patients presented sepsis, 2 presented more mild skin infections and 2 patients died.

**Patients receiving miscellaneous treatments**

In the last group, we included twelve patients with miscellaneous treatments. Three patients received Ulinastatin IV at 7,500U/kg/d to 2,500U/kg/d during a mean of 6 days of treatment. The age range was 1.1 to 9 years and all of them were males. Two patients had TEN and one SJS. No percentage of affected BSA was reported. Time from diagnosis to treatment initiation was one day and the time to objective response was 1 day. Mean time to achieve remission since diagnosis was 5.6 days and mean hospital stay was 12 days. No complications and no deaths were reported. Four patients received treatment based in plasmapheresis. Age in these patients ranged from 3 to14 years. Two patients were females and two males. One patient had diagnosis of SJS/TEN overlap and the rest of them were diagnosed as TEN with an average of 50% BSA. The patients received one to four treatments with an exchange of 1.3 plasma volumes or 2500ml. Time from diagnosis to treatment initiation was not reported. Time to objective response was reported in 2 patients reported being 2 days in both and they presented a time to achieve remission since diagnosis of 10 and 14 days. Hospital stay was reported in 2 patients and was 9 and 13 days. Sanclemente et al. described two patients with SJS and SJS/TEN overlap (25% SBA) that were treated with IV pentoxifylline 12 – 14 mg/kg TID for 5 to 17 days followed by 2 weeks of oral administration. One patient was female and the other was male with a mean age of 2.5 years. Time from diagnosis to treatment initiation was 1 day. One patient reported a time to objective response at day 5 but he also had a relapse the day after because treatment IV was suspended. The mean time to achieve remission since diagnosis was 9.5 days and the mean hospital stay was 19 days. No other complications or deaths were presented. The last three patients received different treatment each one. One was a female 10 year old with TEN treated with Cysclosporin A (1mg/kg/d), Methylprednisone (30mg/kg/d for 3 days) and G-CSF (75Ug). She received this treatment 6 day after her diagnosis. Time to objective response was observed after 3 days and the remission was reported 14 days later. She was released from hospital after 38 days since her admission. A 6 year old female with diagnosis of TEN (80% SBA) was treated initially with prednisone 0.5mg/kg/d during two days after her diagnosis. Her condition worsened and her treatment was change to IVIG 0.5g/kg/d for 4 days. She also presented Sepsis due to Candida parapsillosis. No time to objective response or remission was reported. She was discharged after 60 days. Finally a 17 year old female with SJS received two days after her diagnosis a simultaneous treatment with IVIG 0.5g/kg/d Methylprednisolone for 5Ug/kg/d during 4 and 6 days respectively. Time to objective response was observed after 4 days. There were no complications and the patient was sent home 8 days after her admission.
DISCUSSION

The management of children with SJS and TEN is full of controversy and debate. The first obstacle for management is the difficulty of making an accurate diagnosis. Further, the precise pathophysiological mechanisms of SJS and TEN remain unclear.

It is important to underline that the bulk of the literature about management in SJS and TEN include only adults or adult series with a very small number of children included. The findings of adult studies are not fully extrapolable to care of children. Consequently, we focused our review to specifically address treatment in children. This is the first systematic review to focus on the treatment of SJS and TEN in children.

There are several major findings of this review. The first one is the striking paucity of studies about the management of SJS and TEN in children. We were unable to locate randomized trials of any kind and the observational studies were hindered by low numbers of patients and poor quality of the reports. In second place we found that there is no standardization to classify and evaluate the prognosis and evolution of patients with these entities. Even though SCORTEN has been validated to evaluate patients with SJS and TEN, its use was not reported in any of the included papers.

In the third place, there are no standardized definitions of response to treatment in these diseases. Finally, there is a considerable lack of quality in the description of clinical cases, several of which failed to provide substantial information, probably arising from the fact that there are no minimum standards of reporting for these conditions.

In regard to the information on specific treatments we found that there are two principal trends in the management of SJS and NET in children. The most commonly studied therapy was the use of IVIG. The number of studies and patients evaluated using IVIG is by far the largest of any of the currently studied therapies. Corticosteroid treatment is also frequent but less popular probably as previous studies showed that corticosteroids may increase the number of complications and they failed to be effective in some patients. In spite of this controversy, authors such as Hynes et al. consider that using corticosteroids promptly in suitable doses and in combination with antiviral or antimicrobial agents may stop the progression and improve the evolution of SJS and TEN with relative few complications. There were no noticeable differences regarding time to response, time to remission or length of hospital stay between with papers describing use of corticosteroids versus those describing the use of IVIG. The same findings were observed in the group of dressing with or without surgical debridement and supportive treatment alone; however the last two groups reported larger number of patients with complications including sepsis and skin infections and the duration of hospital stay in these groups were in general higher than in the IVIG and steroids group. The findings in the miscellaneous group are more difficult to interpret as there are not enough papers for each treatment option and the outcomes are quite dissimilar.

It has been suggested that the specific immunological mechanisms including Cytotoxic T Lymphocytes and the membrane-bound Fas Ligand (FasL) on keratinocytes may explain the sudden and widespread apoptosis of epidermal cells in SJS and TEN. However, some evidence also suggest that these might not be the only mechanisms involved, notable as treatments directed to block them (including steroids and IVIG) may have altered severity but certainly do not abolish symptoms. It is not unreasonable to speculate that a multifaceted approach directed to several mechanisms might be the best therapeutic strategy although this is yet to be determined. Based on the information available to date, it is difficult to unconditionally endorse any therapeutic modality in particular but it does seem that the worst option is the use of supportive care alone. Finally, the promising observations regarding the use of novel therapies deserve further attention.

Given the lack of literature providing precise information about the pathogenesis and management of SJS and TEN in children and knowing that designing a randomized controlled study in this population is nearly impossible, it is imperative to create national and international registries to prospectively collect clinical, prognostic, and treatment information about SJS and TEN in a standardized fashion, using uniform criteria to classify, evaluate and manage these conditions.
patients in order to enhance our ability to develop therapeutic guidelines for the care of children with serious cutaneous drug reactions that is guided by evidence.

Given the evidence to date, our findings suggest that choosing either IVIG or steroids together with early withdrawal of the offending drug and energetic treatment support are the best therapeutic choice for children with SJS and TEN.

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REFERENCES


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**TABLE 2**  Characteristics of included studies

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<thead>
<tr>
<th>Reference</th>
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IVIG: Intravenous immunoglobulin

<sup>a</sup> Study also included 8 adults; <sup>b</sup> Five additional patients excluded due to lack of information; <sup>c</sup> Study also included 40 adults
<sup>d</sup> Study also included 5 adults; <sup>e</sup> Study also included 14 adults
TABLE 3  Demographics and outcomes in patients with SJS/TEN according to main treatment received.

<table>
<thead>
<tr>
<th>Treatment/Report category</th>
<th>Patients (N)</th>
<th>Age (Years)</th>
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<th>SJS/TEN/Overlap (N)</th>
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<td>75 / 25</td>
<td>16 / 0 / 0</td>
<td>NR</td>
<td>4^b</td>
<td>7 - 16</td>
<td>NR</td>
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<td>75 / 25</td>
<td>3 / 0 / 1</td>
<td>NR</td>
<td>1 – 3^c</td>
<td>NR</td>
<td>12 – 30^c</td>
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<td>20 / 80</td>
<td>0 / 10 / 0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>19± 3^d</td>
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<td>0 / 3 / 0</td>
<td>1- 2</td>
<td>3 - 7^c</td>
<td>10 – 12</td>
<td>12 - 35</td>
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<td>50 / 50</td>
<td>27 / 2 / 1</td>
<td>NR</td>
<td>9.5^b</td>
<td>9.8 -18</td>
<td>NR</td>
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<tr>
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<td>34 / 66</td>
<td>0 / 1 / 2</td>
<td>1 – 3^c</td>
<td>3 – 7^c</td>
<td>7 - 22^c</td>
<td>6^b</td>
</tr>
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</table>

Unless otherwise stated, all information in reports included in category A are means. In reports included in category B information represents individual patient data.

^a Percentages obtained from 32 patients with available information; ^b Information available in 1 report; ^c Information available in 2 patients; ^d Reported mean ICU stay (SD)
APPENDIX

**SEARCH STRATEGY FOR MEDLINE (OVID):**

1. Epidermal Necrolysis, toxic/ or toxic epidermal necrolysis mp.
2. Lyell’s disease.mp. or Dermatitis, Exfoliative/ or Stevens-Johnson Syndrome/
3. erythema multiforme majus.mp. or Erythema Multiforme/
4. or/1-3
5. STEROIDS/ or steroid.mp.
6. Immunosuppressive Agents/ or immunosuppressant.mp.
7. AZATHIOPRINE/ or azathioprine.mp.
8. CYCLOPHOSPHAMIDE/ or cyclophosphamide.mp.
9. CYCLOSPORINE/ or cyclosporine.mp.
10. THALIDOMIDE/ or thalidomide.mp.
11. Immunoglobulins/ or immunoglobulin.mp.
12. exp THERAPEUTICS/
13. or/5-12
14. 4 and 13