TWELVE YEARS OF LYELL'S SYNDROME IN THE BURN UNIT OF SÃO JOÃO HOSPITAL CENTRE

DOUZE ANS DE SYNDROME DE LYELL DANS LE CTB DU CH SÃO JOÃO

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SUMMARY. Stevens-Johnson syndrome (SSJ) and toxic epidermal necrolysis (TEN) correspond to an acute and rare life-threatening mucocutaneous reaction. We describe the etiology, length of stay, comorbidities and mortality of TEN in our hospital in a retrospective study of 12 years. Twenty-one patients were included in the study. The mean age was 66 years: 57.1% were females. One third had mucosal surface involvement. Median TBSA of epidermal detachment was 66% on day 1. Forty-two per cent had a SCORTEN at admission of 3 and 28.6% had a SCORTEN of 4, which performs 70.6% with SCORTEN ≥5. The most common causes of SJS/TEN in this study were antibiotics. There were a total of 15 deaths (71.4%). All the patients in the antibiotic group died. Patients who needed invasive ventilation had higher mortality (91%) than the non-invasive ventilation group (50%) and the group on spontaneous ventilation (42.8%). The most common complications were sepsis (53%) and renal failure (23%). Highest mortality due to sepsis was in the antibiotic group. When SCORTEN score was calculated for each patient, statistical evaluation showed an increase in mortality with increasing final score. The most crucial interventions are discontinuation of the causative drug and immediate referral to a burn unit, which helps in early diagnosis and decreases mortality. Our study provides insights into the confirmation of the risk of SJS/TEN as well as its treatment. When SSJ/TEN is caused by antibiotics, the suspicion of developing fatal sepsis should be high regardless of the patient’s medical condition.

Keywords: Stevens-Johnson syndrome, toxic epidermal necrolysis, Lyell’s disease, SCORTEN, burn unit

RÉSUMÉ. Le syndrome de Stevens-Johnson et la nécrolyse épidermique toxique (NET) consistent en une réaction cutanéo-muqueuse grave rare. Nous décrivons de manière rétrospective l’étiologie, la durée de séjour, les complications et la mortalité des 21 patients hospitalisés dans notre service pour TEN pendant 12 ans. L’âge moyen des patients était de 66 ans, 57,1% étaient des femmes. Le tiers des patients avaient des atteintes muqueuses. La surface décollée moyenne à J1 était de 66%. Le SCORTEN à l’admission était à 3 chez 42% des patients, 4 chez 28,6% soit 70,6% avec SCORTEN ≤ 5. Les médicaments les plus souvent en cause étaient les antibiotiques. Quinze patients (71,4%) sont décédés, parmi lesquels tous ceux dont le TEN était lié à un antibiotique. Les patients nécessitant une ventilation invasive sont morts dans 91% des cas, ceux sous VNI dans 50% des cas, ceux qui n’ont pas été ventilés dans 42,8% des cas. Les complications les plus fréquentes étaient le sepsis (53%) et l’insuffisance rénale (23%). La mortalité reliée au sepsis était plus fréquente dans le groupe des NET déclenchés par un antibiotique. Elle était reliée au SCORTEN. L’arrêt du médicament en cause et l’hospitalisation immédiate en CTB permettent un diagnostic plus précoce et une réduction de la mortalité. Cette étude donne des éclairages sur les risques de SJS/NET et leur traitement. Quand ils sont dus à un antibiotique, le danger de décéder par sepsis est élevé, quel que soit l’état initial du patient.

Mots-clés: syndrome de Stevens-Johnson, nécrolyse épidermique toxique, syndrome de Lyell, SCORTEN, CTB
Introduction

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a rare, acute, life-threatening systemic condition characterized by a rash that affects the skin and mucosal surfaces. Mucosal involvement can lead to the appearance of ophthalmologic and genito-urinary complications, as well as to respiratory failure and gastro-intestinal bleeding. The affected areas may develop flaccid bullae or irregularly detach (Fig. 1). It is most commonly caused by medications, and more than 100 drugs of various classes have been associated with SJS and TEN (Table I). The median intake time of drugs before symptoms occur is 4 weeks, the most vulnerable time being 8 weeks after the start of drug intake. Today, SJS and TEN are considered a delayed-type hypersensitivity reaction to drugs. Other possible causes include: infectious agents, immunizations, environmental chemicals, radiation therapy and graft-versus-host disease. However, there are still cases of SJS/TEN without any identifiable cause.

The incidence of SJS and TEN is estimated to be one to six and one to two cases per million inhabitants per year, respectively, in the general population. The degree of involved skin is calculated based on the total of blisters, partially or completely detached skin, and Nikolsky positive detachable areas. For the calculation of the involved body surface area (BSA), only undetached and non-detachable erythematous or violet zones are not included. SJS and TEN are components of a continuous spectrum, with TBSA <10% affected considered SJS, TBSA 10 to 30% considered SJS/TEN overlap, and TBSA >30% considered TEN. All three forms of epidermal necrolysis are characterized by widespread blister formation on erythematous skin, and flat, atypical target lesions. Diagnosis of SJS/TEN is confirmed by histopathology: necrotic keratinocytes with separation at the dermal-epidermal junction. The distinction between SJS, SJS/TEN and TEN based on histopathological findings is not possible.

The clinical sequelae of the loss of epidermis associated with SJS/TEN are similar to burns: impaired temperature regulation, increased fluid loss, increased energy expenditure, and increased risk of infection. Thus, supportive therapy includes fluid and electrolyte balance, infection prevention and thermoregulation, similarly to the treatment of a burned patient, in order to promote rapid reepider-
mization of denuded areas. Treatment for SJS/TEN includes prompt cessation of the culprit drug and management in specialized burn units.\(^4\) In the absence of complications, the recovery phase generally lasts from one to three weeks\(^1\) (Fig. 2). The mortality rate varies from 1\% to 5\% for patients with SJS and 30 to 70\% for patients with TEN.\(^5,6\)

In 2000, using data from 165 patients, the toxic epidermal necrolysis-specific severity of illness score (SCORTEN) was developed. It was validated on another sample of 75 patients.\(^7\) SCORTEN is based on evaluation during the first 24 hours of admission. Variables include age (≥40 years), heart rate (≥120 beats/min), cancer/hematologic malignancy, TBSA involvement (>10\%), blood urea nitrogen level (BUN>28 mg/dl), serum glucose level (>252 mg/dl), and serum bicarbonate (HCO\(_3\) <20 mEq/l).\(^7\) Each variable contributes one point to SCORTEN, with the predicted mortality increasing with score, as shown in Table II.\(^7\)

In addition, lactate dehydrogenase (LDH), late withdrawal of causative drug, and delayed referral to a burn centre have also been shown to be important predictors of mortality.\(^8,9,10\)

### Methods

This is a retrospective study including all patients who were admitted to our burn centre with biopsy-confirmed SJS/TEN between January 2006 and May 2018. The data collected included demographic data and SCORTEN scores for day 1. Patient demographic data were described using descriptive statistics. The primary outcome of the study was in-hospital mortality. Secondary endpoints included the association of SCORTEN scores with length of stay (LOS), length of stay in the intensive care unit (LOS-ICU), in-hospital complications such as acute kidney injury (AKI) or infection, and the use of corticosteroids or cyclosporine.

AKI was defined using the Acute Kidney Injury Network criteria, including increased serum creatinine, decreased urine output, and the need for renal replacement therapy in a patient without pre-existing renal impairment.

Infection was defined as antimicrobial use associated with a positive culture (blood, urine, respiratory or wound).

The patients were treated by plastic surgeons in collaboration with anaesthesiologists and, when needed, dermatologists, ophthalmologists, gynaecologists, otolaryngologist and physiotherapists.

<table>
<thead>
<tr>
<th>SCORTEN parameter</th>
<th>Individual score</th>
<th>SCORTEN (sum of individual scores)</th>
<th>Predicted mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age&gt;40 years</td>
<td>Yes=1, No=0</td>
<td>0–1</td>
<td>3.2</td>
</tr>
<tr>
<td>Comorbid malignancy</td>
<td>Yes=1, No=0</td>
<td>2</td>
<td>12.1</td>
</tr>
<tr>
<td>Tachycardia (&gt;120/min)</td>
<td>No=0</td>
<td>3</td>
<td>35.8</td>
</tr>
<tr>
<td>Initial surface of epidermal detachment &gt;10%</td>
<td>Yes=1, No=0</td>
<td>4</td>
<td>58.3</td>
</tr>
<tr>
<td>Serum urea &gt;10 mmol/l or 28mg/dL</td>
<td>Yes=1, No=0</td>
<td>≥ 5</td>
<td>90</td>
</tr>
<tr>
<td>Serum glucose &gt;14 mmol/l or &gt;252mg/dL</td>
<td>Yes=1, No=0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicarbonate &lt;20 mmol/l</td>
<td>Yes=1, No=0</td>
<td></td>
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</tr>
</tbody>
</table>
dle and margin wound representative samples were taken and sent for histopathological analysis. Non-essential medications were stopped upon arrival. Antibiotic treatment was started only for proven infection. All the patients received supportive therapy. The blisters were aspirated under general anaesthesia if necessary. The detached epidermis was used as a biological dressing. The wounds were covered with fat gauzes soaked in a 0.02% chlorhexidine solution until 2015. After that, the wounds were covered with fat gauzes and iodopovidone. Patients did not receive glucocorticoid treatment, unless the patient was referred to us on glucocorticoid and then the dose was slowly decreased to zero.

Results

A total of 21 patients were included in the study. The mean age was 66 years and 57.1% were females. One third of the patients had involvement of the mucosal surfaces. The most common comorbidities were hypertension, diabetes, obesity, chronic renal disease and HIV. One of our patients had multiple myeloma and another had a history of recent bilateral mastectomy due to breast cancer. The median TBSA of epidermal detachment was 66% on day 1. Forty-two per cent had a SCORTEN at admission of 3 and 28.6% had a SCORTEN of 4, which performs 70.6% with SCORTEN ≥ 5.

Of the 21 patients included in this study, only 1 had SJS/TEN overlap, and 20 had TEN. None of the admissions in the study group corresponded to SJS. The median LOS was 17 days, with a median LOS-ICU of 13 days. The median days of delay in referral to the burn centre was 4 days.

The most common causes of SJS/TEN in this study were: antibiotics reported 9 times (43%) and allopurinol reported 6 times (28.6%). Other causes included AINEs, neuroleptics, antidepressives, lenalidomide and paracetamol.

There were a total of 15 deaths (71.4%) in this study population. All the patients in the antibiotic group died. The allopurinol group had a mortality of 50%. The highest mortality was found in the over 65s age group. We had no deaths in the under 45s group. Mortality increased with the increase in SCORTEN: 20% mortality with SCORTEN ≤ 2 and 87.5% with SCORTEN ≥3.

As shown in Fig. 3, the AUROC curve for day 1 SCORTEN predicting mortality is 0.883, which conveys a relatively strong discriminative power for the SCORTEN model.

A delay in patient referral superior to 48 hours corresponded to a mortality rate of 77.8%, while referral in the first 24 hours corresponded to a mortality rate of 62.8%.

Approximately half of our patients received intravenous immunoglobulin (IVIG) therapy, with no differences observed in mortality (~60% of mortality rate in both groups).

Invasive ventilation was needed at some point in 57%. This group had higher mortality (91%) than the non-invasive ventilation group (50%) and the group on spontaneous ventilation (42.8%).

The most common complications were sepsis (53%) and renal failure (23%).

Highest mortality due to sepsis was in the antibiotic group, when compared to all other SJS/TEN causing agents.

Discussion

SJS and TEN still represent a major challenge. There is currently no specific treatment. The most crucial interventions are discontinuation of the offending drug and prompt referral to a burn unit for...
optimized supportive care. It has to be recognized that drugs with a long half-life seem to be associated with a higher mortality rate. Depending on the centres and their experience, fat gauze with iodopovidone or silver-releasing wraps/dressings are the therapy of choice, although studies comparing local treatments are lacking. Our practise, since 2015, is to cover the wounds with fat gauzes and iodopovidone, preserving, if possible, the detached epidermis with satisfactory results.

The importance of a quick referral to a burn centre is due to the fact that increased mortality may be seen in the event of delayed admission of 7 days or more after onset of symptoms. Our results show that a delay in patient referral superior to 48 hours corresponded to an increase in mortality rate of 77.8% (while referral in the first 24 hours corresponded to a mortality rate of 62.8%).

Our patients did not receive glucocorticoid treatment, unless the patient was referred to us on glucocorticoid and then the dose was slowly decreased to zero. It is known that corticosteroids bear a high risk for bacterial infections/sepsis and do not seem to be superior to supportive care only.

Approximately half of our patients received intravenous immunoglobulin (IVIG) therapy, with no differences observed in mortality. However, the sensitivity analysis based on multiple studies shows a trend towards a beneficial effect of IVIG with respect to mortality.

According to the literature, cyclosporine A seems to be a promising therapy, though it is not an option for patients with renal failure and/or immune deficiency.

The onset of SJS/TEN is known to be higher in the adult age, probably because of higher intake of drugs in comparison to children and adolescents. In our study, the median age of patients was 66 years. We did not include paediatric patients who were referred for paediatric surgery in our hospital.

It is known that women have about an equal or slightly higher incidence of SJS, SJS/TEN, TEN than men. This is concordant with our study.

Only one third of our patients had mucosal involvement, which is contrary to the literature: mucosal involvement occurs in the majority of patients.

The most common complications we observed in our patients was sepsis (53%). Highest mortality due to sepsis was in the antibiotic group, when compared to all other SJS/TEN causing agents. In fact, septicemia is still a leading cause of morbidity and fatality. The probability of positive blood cultures was correlated with delayed admission to the specialized burn centre of 7 or more days. All patients in our study, whose causative agent was an antibiotic, died.

This should lead us to take into account the high probability of death when the agent is an antibiotic. This may be due to the fact that there is already a septic focus in a patient who develops an inflammatory systemic disease, increasing the likelihood of sepsis. This is corroborated by other publications. Hermiz et al. analyzed the effect of hospital-acquired
infections on mortality in SJS/TEN patients. They observed that antibiotics were the leading cause of death in patients with drug-induced SJS/TEN. These patients were at a higher risk of developing severe septicemia.\textsuperscript{15} Monteiro et al. concluded that in antibiotic-associated SJS/TEN, it was responsible for the fatal outcome.\textsuperscript{2} Similar findings with a mortality rate of 38\%, mostly attributed to sepsis, were demonstrated in a German study, where antibiotics were the most frequent cause of fatality.\textsuperscript{16}

The second most frequent complication we observed was renal failure (23\%), slightly higher than that described in the literature (14.9\%).\textsuperscript{1}

In a retrospective larger cohort study, 25\% of patients had to be mechanically ventilated, half of whom died. They also found that the extent of detached BSA on hospital admission was strongly associated with invasive ventilation and independent from variables reflecting organ dysfunctions.\textsuperscript{17} In our study, invasive ventilation was needed at some point in 57\%. This group had higher mortality (91\%) than the non-invasive ventilation group (50\%) and the group on spontaneous ventilation (42.8\%). Mechanical ventilation is associated with a poor outcome. Prompt identification of STS/TEN patients at higher risk of intubation could help guide their early management, particularly for those with bronchial epithelial lesions.

The mortality rate varies from 30 to 70\% in TEN.\textsuperscript{6} The increased mortality observed in our patients (71.4\%) can be explained by the exclusion of patients not hospitalized in the burn unit. This excludes cases of Stevens-Johnson (usually included in international studies), which has lower mortality.\textsuperscript{5} In our hospital, SJS is treated in other hospital departments, such as Dermatology. Paediatric patients were not included in our study. They usually have better outcomes.\textsuperscript{18} Most of our patients had various chronic diseases, including HIV. In a South African study of SJS/TEN, HIV infection was shown to be the major factor associated with a higher risk of fatal outcome (odds ratio 6).\textsuperscript{19} The majority had antibiotics as the causal agent, which is associated with bad outcome.\textsuperscript{1} Admission delay in our burn unit was 4 days (range 0-14), almost twice that of other studies,\textsuperscript{1} but similar to the results in another Portuguese hospital.\textsuperscript{20}

\textbf{Conclusions}

SCORTEN seems to be an accurate scoring system for estimation of mortality rate. When SJS/TEN is caused by antibiotics, the suspicion of developing fatal sepsis should be high, irrespective of the patient’s medical condition. Interdisciplinary cooperation is very important. Clinicians must remain vigilant about drug hypersensitivity to prevent SJS, SJS/TEN and TEN and about correctly referring identified cases to specialized units.

\textbf{BIBLIOGRAPHY}

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