**UK guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016**

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**Footnote**:

*This is a new set of guidelines prepared for the British Association of Dermatologists (BAD) Clinical Standards Unit, which includes the Therapy & Guidelines Sub-committee. Members of the Clinical Standards Unit that have been involved are: PM McHenry [Chairman T&G], JR Hughes, M Griffiths, K Gibbon, AJ McDonagh, DA Buckley, I Nasr, VJ Swale, CE Duarte Williamson, NJ Levell, T Leslie, E Mallon, S Wakelin, S Ungureanu, P Hunasehally, M Cork, K Towers [British National Formulary], J Donnelly [British National Formulary], C Saunders [British Dermatological Nursing Group], LS Exton [BAD Information Scientist], AG Brain [BAD Clinical Standards Administrator], MF Mohd Mustapa [BAD Clinical Standards Manager].*

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**CONFLICTS OF INTEREST**:

JKGD (1) grant/research support - Dompe pharmaceuticals, SiFi Pharmaceuticals (non-specific); MA-J (1) commissioned work – Genus Pharmaceuticals (non-specific); (2) sponsorship to conferences – Abbvie, Janssen-Cilag, Pfizer, Galderma, Steifel (non-specific); (3) clinical trials - Zymogenetics, Pfizer, Genentech, Johnson & Johnson, Centocor, Novartis (non-specific); (4) grant/research support – Emblation (non-specific); (5) developed non-profit website [www.drugrash.co.uk](http://www.drugrash.co.uk) to assist clinicians in management of drug allergy (specific). None of the authors have received commercial support from the manufacturers of any medication used in the management of SJS/TEN.

**Key words**: Stevens-Johnson syndrome, toxic epidermal necrolysis, drug hypersensitivity, management, guidelines

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| NICE_Accreditation_max | NICE has accredited the process used by the British Association of Dermatologists to produce guidelines. Accreditation is valid for 5 years from May 2010 and has been extended by agreement to May 2016. More information on accreditation can be viewed at [*www.nice.org.uk/accreditation*](http://www.nice.org.uk/accreditation).  For full details of our accreditation visit: [*www.nice.org.uk/accreditation*](http://www.nice.org.uk/accreditation)*.* |

**1.0 Purpose and scope**

The overall objective of the guideline is to provide up-to-date, evidence-based recommendations for the diagnosis and management of the full spectrum of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and SJS-TEN overlap in adults during the acute phase of the disease.

The document aims to:

* offer an appraisal of all relevant literature up to June 2015, focusing on any key developments
* address important, practical clinical questions relating to the primary guideline objective, i.e. accurate diagnosis and identification of cases and suitable treatment
* provide guideline recommendations
* discuss areas of uncertainty, potential developments and future directions

SJS/TEN is rare and few health care professionals are confident in the recognition and management of the disorder. There is widely divergent practice amongst different specialities and healthcare settings, and limited information on outcomes. These guidelines, aim to provide recommendations on the diagnosis and management of SJS/TEN, to inform clinical decision-making and, when justified by evidence, to standardize practice. The breadth of this document should be sufficient to assist clinicians of all relevant specialities in the management of patients with SJS/TEN. The recommendations will also inform pathways of care to optimize healthcare delivery and highlight key areas of uncertainty for future research.

In this guideline, the term SJS/TEN encompasses the full spectrum of the disease, i.e. SJS, SJS-TEN overlap and TEN (see section 7.2 for clinical definition of the separate entities). The guideline is presented as a detailed review with highlighted recommendations for practical use (see section 18.0), in addition to the development of a new Patient Information Leaflet (PIL; available on the BAD website, [www.bad.org.uk](http://www.bad.org.uk)). Unless otherwise specified, recommendations apply to all forms of the disease.

**1.1 Exclusions**

This guideline does not cover paediatric patients. An addendum to this guideline addressing the needs of paediatric patients with SJS/TEN is planned. The evidence for treatment of children differs from that of adult patients, and will be considered separately.

The management of long-term sequelae of SJS/TEN is not considered in this document.

**2.0 Stakeholder involvement and peer review**

The guideline development group consisted of consultant dermatologists (DC, SAW, HYL, JS, CBB, MAJ, KMTW, GAEW, CHS), including oral (JS) and urogenital specialists (SAW, CBB), a histopathologist (MP), burns/plastic surgeon specialists (PD, GW, MS), a burns anaesthestist (RVM), intensive care specialists (AV, RVM), an ophthalmologist (JKGD), a dermatological clinical nurse specialist (DB), and a patient (PW). The draft document went out for consultation to the BAD membership, British Dermatological Nursing Group (BDNG), Primary Care Dermatological Society (PCDS), British Burn Association (BBA), British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS), Royal College of Ophthalmologists (RCOphth), Association of Anaesthetists of Great Britain and Ireland (AAGBI), Intensive Care Society and SJS Awareness UK. The comments received were actively considered by the GDG. Following further review, the amended draft was recirculated to the stakeholders for comments and the finalized version peer-reviewed by the Clinical Standards Unit of the BAD (made up of the Therapy & Guidelines Sub-committee) prior to publication.

**3.0 METHODOLOGY**

This set of guidelines has been developed using the British Association of Dermatologists’ recommended methodology1 and with reference to the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument [[www.agreetrust.org](http://www.agreetrust.org)].2 Recommendations were developed for implementation in the NHS using a process of considered judgment based on the evidence. A series of specific questions were developed within the scope of the guideline; for each question, PubMed, MEDLINE and EMBASE databases and the Cochrane Library were searched for meta-analyses, randomized and non-randomized controlled clinical trials, open studies and case series to June 2015. The literature was searched for evidence to address the questions. The search terms and strategies are detailed as a web appendix. Additional relevant references were also isolated from citations in reviewed literature, as well as specific targeted searches for hypersensitivity testing, causative drugs, diagnostic and prognostic indicators, topical treatments, oral/mouth, growth factors and granulocyte colony-stimulating factor (G-CSF) and analgesia. The lead authors screened the identified titles and those relevant for first-round inclusion were selected for further scrutiny. All co-authors then reviewed the abstracts for the shortlisted references and the full papers of relevant material were obtained; disagreements in the final selections were resolved by discussion with the entire guideline development group (GDG). In section 13, active interventions were assessed only if studies recruited at least eight SJS/TEN patients into the treatment group. The structure of the guidelines was then discussed, with headings and sub-headings decided; different co-authors were allocated separate sub-sections. Each co-author then performed a detailed appraisal of the selected literature, and all sub-sections were subsequently collated and edited to produce the final guideline.

**4.0 Limitations of the guideline**

This document has been prepared on behalf of the BAD and is based on the best data available when the document was prepared. It is recognized that under certain conditions it may be necessary to deviate from the guidelines and that the results of future studies may require some of the recommendations herein to be changed. Failure to adhere to these guidelines should not necessarily be considered negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence.

**5.0 Plans for guideline revision**

The proposed revision date for this set of recommendations is scheduled for 2021; where necessary, important interim changes will be updated on the BAD website.

**6.0 BACKGROUND**

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe muco-cutaneous reactions, usually to drugs, characterized by blistering and epithelial sloughing.3 The two terms describe phenotypes within a severity spectrum, in which SJS is the less extensive form and TEN is the more extensive. The incidence of SJS/TEN is approximately one to two cases per million per year.4,5 Although rare, SJS/TEN is a devastating disease; in severe cases the acute phase may be accompanied by a variety of systemic complications, including multi-organ failure. The mortality for SJS is less than 10%, with the figure rising to 30% for TEN, and overall SJS/TEN mortality is about 22%.6 As well as carrying an appreciable mortality, survivors of the acute illness often develop significant long-term sequelae.7

SJS/TEN is characterized by widespread epithelial keratinocyte apoptosis and necrosis, a process initiated by drug-induced cytotoxic T lymphocytes (CTLs).8 Major histocompatibility complex (MHC) class I-restricted drug presentation leads to clonal expansion of CD8+ CTLs9 which infiltrate the skin, while soluble factors induce keratinocyte apoptosis.10 Pro-apoptotic molecules, including tumour necrosis factor-, interferon- and inducible nitric oxide synthase, may link drug-induced immune responses to keratinocyte damage.11 Although soluble Fas ligand, perforin and granzyme have all been implicated in triggering keratinocyte programmed cell death,12,13 current evidence favours granulysin as the key mediator of apoptosis in SJS/TEN.14 A study by Chung *et al*. demonstrated the presence of high concentrations of secretory 15 kDa granulysin in TEN blister fluid, while injection of 15 kDa granulysin into mouse skin induces keratinocyte apoptosis, mimicking SJS/TEN.14

**7.0 DIAGNOSIS, INITIAL ASSESSMENT, DRUG CAUSALITY AND PROGNOSIS IN SJS/TEN**

**7.1** **What are the clinical features of SJS/TEN?**

SJS/TEN is an acute, severe dermatosis characterized by epidermal loss and multi-site mucositis, accompanied by systemic disturbance. A study by Revuz *et al*. of 87 consecutive patients managed on a specialist unit gives a detailed description of the clinical features observed in SJS/TEN.15 In general, a prodrome of fever, malaise and upper respiratory tract symptoms precedes the eruption by several days. Ocular inflammation may also develop before the skin signs. Cutaneous pain is a prominent early feature in SJS/TEN, and the presence of this symptom should alert the physician to incipient epidermal necrolysis. Clinical observation in the Revuz *et al.* series demonstrated a wide variation in the type of lesion and degree of skin involvement. The earliest lesions are atypical targets (Figure 1) and/or purpuric macules (Figure 2). Initial sites of involvement are commonly the upper torso, proximal limbs and face. Thereafter lesions spread to involve the rest of the trunk (Figure 3) and distal limbs. Involvement of the palms and soles is often prominent (Figure 4). Large areas of confluent erythema develop in severe cases (Figure 5). Lesional skin is tender to touch; minimal shearing forces will cause the epidermis to peel back (Figure 6). This fragility is demonstrated by the Nikolsky sign, in which gentle lateral pressure causes lesional, detachable epidermis (as opposed to detached epidermis) to slide over the dermis. Although not specific for SJS/TEN (it is also positive in pemphigus) the Nikolsky sign is a helpful clinical indicator of epidermal necrolysis. Involved areas expand and coalesce, reaching a maximum 5 to 7 days after disease onset. Blistering ensues in which necrotic epidermis separates from underlying dermis producing flaccid bullae (Figure 7). Extensive necrolysis results in the detachment of sheets of epidermis leaving areas of exposed dermis (Figure 8). Denuded dermis exudes serum, becomes secondarily infected and readily bleeds. Involvement of the mucous membranes of the eyes (Figure 9), mouth (Figure 10), nose and genitalia (Figure 11) is usually an early feature and leads to an erosive and haemorrhagic mucositis. In Revuz *et al.*’s series of 87 SJS/TEN patients, 97% developed erosive mucous membrane lesions; oral involvement was observed in 93% of patients, ocular in 78%, genital in 63%, and all three sites in 66%.15 Respiratory tract epithelial necrolysis can occur resulting in bronchial obstruction and ventilatory compromise; necrolysis of gastrointestinal epithelium leads to profuse diarrhoea. Acute kidney injury may occur in the early phase of SJS/TEN due to hypoperfusion and acute tubular necrosis. Mild elevation of liver enzymes is common but significant hepatic impairment is rare.

Despite the striking clinical presentation of SJS/TEN, a number of disorders can present with blistering of the skin and mucous membranes; the clinical differential diagnosis includes pemphigus, pemphigoid, other immunobullous disorders, and erythema multiforme major (EMM) (see Table 1).

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| Erythema multiforme major |
| Pemphigus vulgaris |
| Mucous membrane pemphigoid |
| Bullous pemphigoid |
| Paraneoplastic pemphigus |
| Bullous lupus erythematosus |
| Linear IgA bullous dermatosis |
| Generalised bullous fixed drug eruption |
| Bullous acute graft-versus-host disease |
| Staphylococcal scalded skin syndrome |
| Acute generalised exanthematous pustulosis |

**Table 1.** Differential diagnosis of SJS/TEN

**7.2 What are the recognized clinical phenotypes in SJS/TEN?**

In a study from Bastuji-Garin *et al.,* a group of physicians experienced in managing SJS/TEN reviewed the clinical photographs of more than 200 patients and categorized the cases according to type of cutaneous lesion and extent of maximal epidermal detachment:16

* **SJS** (epidermal detachment less than 10% body surface area (BSA) plus widespread purpuric macules or flat atypical targets).
* **Overlap SJS-TEN** (detachment of 10% to 30% BSA plus widespread purpuric macules or flat atypical targets).
* **TEN with spots** (detachment greater than 30% BSA plus widespread purpuric macules or flat atypical targets).
* **TEN without spots** (detachment greater than 30% BSA with loss of large epidermal sheets without purpuric macules or target lesions).

There is acknowledgement that these phenotypic categories are not mutually exclusive; cases with features from two or more of the above groups may occur.17

At the less severe end of the spectrum, differentiation of SJS from EMM can be difficult. In EMM, there is mucous membrane involvement and cutaneous blistering with epidermal detachment of less than 10% BSA. However, in contrast to SJS, the skin lesions in EMM consist of typical targets or raised atypical targets, predominantly localized on the limbs and extremities. Distinguishing EMM from SJS/TEN has causality implications: EMM is mostly related to Herpes simplex virus (HSV) reactivation and rarely to drugs; SJS/TEN is usually triggered by a drug, rarely by an infection.17,18 Mycoplasma-induced SJS is reported and in some cases, which are mostly children, may be characterized by a phenotype of predominantly mucous membrane involvement with little or no cutaneous lesions. This clinically atypical form of SJS has been termed ‘mycoplasma pneumoniae-associated mucositis’ (MPAM).19

**7.3 What are the histopathological features of SJS/TEN?**

Although a diagnosis of SJS/TEN is suggested by the physical signs, histopathology of a skin biopsy is necessary to support the clinical assessment and exclude other blistering dermatoses (see Table 1). Histologically, there is variable epidermal damage ranging from individual cell apoptosis to confluent epidermal necrosis. Epidermal changes are associated with basal cell vacuolar degeneration and subepidermal vesicle or bulla formation. Adnexal structures such as sweat ducts and hair follicles are occasionally involved. Within the dermis, there is often only a mild, predominantly perivascular infiltrate of lymphocytes and histiocytes with small numbers of eosinophils present in some cases (Figure 12).20

**7.4 What initial assessment should be undertaken in a patient presenting with SJS/TEN to secondary/tertiary care?**

If SJS/TEN is suspected, discontinue any potential drug immediately. The patient should undergo an evaluation of the critical disease components. Clinical examination includes an appraisal generic to any acutely ill patient, as well as assessments specific to SJS/TEN. Institution of an immediate management protocol is necessary as soon as the patient has been assessed.

**Recommendations: *(Strength of recommendation D (GPP); level of evidence 4) (See Appendix 1)***

Take a detailed history from the patient (and/or relatives) with specific reference to the following:

* Ask about symptoms suggestive of SJS/TEN including a prodromal illness (fever, malaise, upper respiratory tract symptoms); onset of a painful rash, initially on the face and chest; involvement of mucosal sites (eyes, mouth, nose, genitalia).
* Note the date when the rash first appeared and document progression of the eruption.
* Ask about symptoms indicating involvement of the respiratory tract: cough, dyspnoea, bronchial hypersecretion, haemoptysis.
* Ask about symptoms indicating bowel involvement: diarrhoea, abdominal distension.
* Determine the index date (date of onset of the adverse reaction) by asking when the patient developed the first symptom or sign of the disorder, for example sore throat, rash, skin pain, sore eyes/mouth.
* Record previous or on-going medical problems; ask specifically about a history of recurrent HSV infections and chest infections.
* Record **all** medicines taken over the previous 2 months , including over-the-counter and complementary/alternative therapies; document the date treatments were started, and the date, when appropriate, of dose escalation; document the date when drugs were stopped. Note if there has been a brand switch or any medication errors.
* Record any previous history of drug allergies, including details of the reaction type.
* Actively consider other causes of severe skin disease characterized by blistering and involvement of mucus membranes (see Table 1).

* Perform a full physical examination, including baseline body weight. Record the vital signs and measure oxygen saturation with a pulse oximeter.
* Look for target lesions, particularly atypical targets, purpuric macules, blisters, and areas of epidermal detachment.
* Examine all mucosal sites looking for mucositis, blisters and erosions.
* Record the extent of erythema and the extent of epidermal detachment separately on a body map (Figure 13); for each parameter estimate the percentage of BSA involved using the Lund and Browder (L&B) chart. Detachment should include detachable epidermis (i.e. Nikolsky positive) as well as detached epidermis; it is this figure, rather than the amount of erythema, which has prognostic value.

The following investigations should be undertaken:

* Full blood count (FBC), ESR, CRP, urea and electrolytes (U&E), magnesium, phosphate, bicarbonate, glucose, liver function tests (LFT) and coagulation studies, mycoplasma serology.
* Chest X-ray.
* A biopsy from lesional skin, just adjacent to a blister, and send for routine histopathology; a second biopsy taken from peri-blister lesional skin should be sent unfixed for direct immunofluorescence to exclude an immunobullous disorder.
* Swabs from lesional skin for bacteriology.
* Organize photographs of the skin to show type of lesion and extent of involvement.

Initiate a primary management plan:

* Discontinue any potential culprit drug causing SJS/TEN immediately (see Table 2).
* Establish peripheral venous access; where possible, insert the cannula through non-lesional skin; commence appropriate intravenous fluid resuscitation if clinically indicated (see section 8.3). A fluid chart should be initiated.
* Ascertain if the patient can maintain adequate hydration and nutrition orally; if this is not possible, insert a naso-gastric tube and institute naso-gastric feeding (see section 8.4).
* Insert a urinary catheter when urogenital involvement is causing significant dysuria or retention. A urinary catheter will also permit accurate output monitoring to assist fluid replacement.

**7.5 Is there a clinical method of determining drug causality in SJS/TEN?**

SJS/TEN is primarily a drug-induced phenomenon, with a culprit drug being demonstrated in approximately 85% of cases.21 Identification of the causative agent may be straightforward in cases where a single drug is implicated, but difficulties are posed by the patient who has been exposed to multiple drugs. Early withdrawal of the suspected agent is mandatory, as this decreases the risk of death.22 The patient’s other regular medicines should be continued.

Notoriety of specific drugs in causing SJS/TEN can be determined from population pharmacovigilance data and is useful in identifying a likely culprit.6,23-28 Two multinational case-control studies have evaluated drug causation risk: the first, conducted from 1989 to 1995, included 372 cases and 1720 controls;23 the second, carried out between 1997 and 2001, consisted of 379 cases and 1505 controls.6 From case-control studies, a list of drugs which are strongly associated with the induction of SJS/TEN has been drawn up; these medicines are responsible for one-half of all cases (see Table 2). Paracetamol, aspirin, ibuprofen, and corticosteroid have an unclear association, but are likely to be confounders used to treat prodromal symptoms of SJS/TEN.

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| Allopurinol |
| Carbamazepine |
| Lamotrigine |
| Nevirapine |
| Oxicam NSAIDs |
| Phenobarbital |
| Phenytoin |
| Sulfamethoxazole and other sulfur antibiotics |
| Sulfasalazine |

**Table 2.** Commonest drugs causing SJS/TEN

An algorithm, termed ALDEN (ALgorithm of Drug causality in Epidermal Necrolysis), has been developed to help define drug causality in SJS/TEN.21 ALDEN is generally used as a tool for retrospective assessment of drug causality, and not for use in the acute phase of illness. However, the key parameters described in ALDEN can be applied as a useful framework for determining drug culpability in clinical practice.

**Recommendations: *(Strength of recommendation D; level of evidence 3)***

* List all medications (including OTC preparations) taken by the patient over a period of 2 months prior to the onset of symptoms. Use multiple sources (including patient, relatives, GP, pharmacist) to obtain a full drug history.
* Delineate a timeline for each drug, identifying the date the drug was commenced and, when appropriate, discontinued. Tools to facilitate timeline analysis include web-based freeware such as [www.drugrash.co.uk](http://www.drugrash.co.uk). A latent period between the initial drug intake and onset of SJS/TEN always occurs; 5 to 28 days following drug initiation is the most likely period, unless there is a history of a previous reaction to the same drug, in which case the latency may be shorter.
* Estimate the probability that the drug was present in the body at the onset of the reaction by taking into consideration pharmacokinetic parameters of the drug (e.g. half-life), any renal or hepatic dysfunction and possible drug interactions, which might lead to higher or lower levels of drug in the body.
* For each drug taken by the patient, document any previous exposures and any previous adverse reactions. Implication of a particular medicine is more likely if the patient gives a past history of a drug hypersensitivity reaction with the same or similar drug.
* For each drug taken by the patient, assess notoriety to cause SJS/TEN (see Table 2).
* When a causative drug cannot be identified, consider other possible etiological factors, such as mycoplasma infection.

**7.6 What is the value of prognostic scoring in SJS/TEN?**

In severe cases of SJS/TEN the acute systemic sequelae lead to multi-organ failure and death. Papers investigating potential prognostic markers in SJS/TEN have identified several factors associated with death, including: delayed transfer to a specialist unit, increasing patient age, increasing total BSA involvement, presence of septicaemia and occurrence of granulocytopenia.29,30

In 2000 Bastuji-Garin *et al.* published a validated prognostic scoring system for SJS/TEN, called SCORTEN, which uses seven clinical parameters to predict probability of hospital mortality31 (see Tables 3 & 4). In SCORTEN, one point is attributed to each of the seven parameters, with increasing scores predicting higher mortality rates.

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| Age greater than 40 years |
| Presence of malignancy |
| Heart rate greater than120 beats/min |
| Epidermal detachment greater than10% BSA at admission |
| Serum urea greater than10mmol/L |
| Serum glucose greater than14 mmol/L |
| Bicarbonate level less than 20mmol/L |

**Table 3.** SCORTEN calculation.

|  |  |
| --- | --- |
| Number of parameters | Predicted mortality |
| 0 | 1% |
| 1 | 4% |
| 2 | 12% |
| 3 | 32% |
| 4 | 62% |
| 5 | 85% |
| 6 | 95% |
| 7 | 99% |

**Table 4.** SCORTEN predicted mortality.

A longitudinal assessment of 144 patients demonstrated that SCORTEN rises slightly during hospitalisation, with a significant difference between day 1 and day 4.32 Since the publication of Bastuji-Garin *et al.*’s original paper, retrospective analysis of several SJS/TEN case series has confirmed SCORTEN’s ability to predict mortality accurately.33-37

**Recommendation: *(Strength of recommendation C; level of evidence 2+)***

* SCORTEN should be calculated in all SJS/TEN patients within the first 24 hours of admission.

**8.0 INITIAL MANAGEMENT AND SUPPORTIVE CARE**

**8.1 What care setting is needed for the management of SJS/TEN patients?**

Extensive epidermal detachment in SJS/TEN is accompanied by thermoregulatory dysfunction, large insensible fluid loss and haemodynamic instability. Other sequelae of acute skin failure include anaemia, leucopenia, renal impairment, liver dysfunction and systemic sepsis, the last being the most frequent cause of death. It is therefore recommended that patients with large areas of epidermal loss (greater than 10% BSA) are admitted to a specialist intensive care unit (ICU) for critical care management and specialist nursing (see SJS/TEN Pathway of Care). Since the cutaneous defect in SJS/TEN is analogous to a large superficial burn, many patients are transferred to a Burn Centre which can deliver both intensive supportive management as well as skin-directed therapy. Staff, facilities and standard operating procedures on a Burns Centre are well defined for the management of skin failure and extensive skin loss. Three studies and a systematic review of TEN cases have demonstrated that rapid admission to a Burns Centre is associated with improved survival, whilst delayed transfer is accompanied by increased mortality.29,38,39 40

Provision of the many specialist services necessary for managing SJS/TEN cases engenders a need for multi-disciplinary team (MDT) working. The SJS/TEN MDT should be co-ordinated by a specialist in skin failure, usually dermatology and/or plastics, and should include clinicians from intensive care, ophthalmology and skin care nursing. Within an ICU (Specialist or Burn Centre) the patient should be nursed in a side room to facilitate barrier nursing and to allow the immediate environment to be heated. Studies in burns patients have demonstrated that, at room temperature, energy expenditure increases by 40% of basal metabolic rate (BMR) with skin loss of 10% BSA, while at 80% BSA skin loss energy expenditure increases by 120% of BMR.41,42 The same thermoregulatory dysfunction occurs in extensive epidermal necrolysis and therefore a raised ambient temperature is necessary in SJS/TEN patient care to reduce energy consumption and associated metabolic stresses.

**Recommendations: *(Strength of recommendation D (GPP); level of evidence 4)***

* SJS/TEN patients with greater than 10% BSA epidermal loss should be admitted without delay to a Burn Centre or to an ICU with experience of treating patients with SJS/TEN and facilities to manage the logistics of extensive skin loss wound care.
* The SJS/TEN multi-disciplinary team should be co-ordinated by a specialist in skin failure, usually dermatology and/or plastic surgery, and should include clinicians from intensive care, ophthalmology and specialist skin care nursing. Additional clinical input to the MDT may be required from respiratory medicine, gastroenterology, gynaecology, urology, oral medicine, microbiology, pain team, dietetics, physiotherapy and pharmacy.
* SJS/TEN patients must be barrier-nursed in a side room controlled for humidity, on a pressure-relieving mattress with the ambient temperature raised to between 25° to 28 °C.

**8.2 What skin management regimen should be followed in SJS/TEN?**

In SJS/TEN, necrotic epidermis is prone to detach from underlying dermis, therefore careful handling of the skin in these patients is essential. In particular, care must be taken to minimize shearing forces applied to the skin, especially when moving and positioning the patient (anti-shear handling).43 Day-to-day bedside care is preferably undertaken by specialist nurses familiar with skin fragility disorders.43 Other attending clinicians, who are unfamiliar with the problems of epidermal detachment, should be warned before examining the patient. Despite careful nursing, lesional epidermis in SJS/TEN often peels away, especially at pressure areas, to leave zones of denuded dermis.

There are differing approaches to local management of lesional skin with no good evidence as to which is superior.

In the conservative approach, detached epidermis is left *in situ* to act as a biological dressing for the underlying dermis. In cases where bullae are prominent, blister fluid should be aspirated or expressed and the blister roof allowed to settle onto the underlying dermis.44-46 Frequent application of a bland emollient to the whole skin is helpful during the acute phase of SJS/TEN to support barrier function, reduce transcutaneous water loss and encourage re-epithelialisation.44 The use of an appropriate dressing on exposed dermis will reduce fluid and protein loss, limit microbial colonisation and help pain control. Covering the denuded skin may also accelerate re-epithelialisation. Once active blistering and epidermal detachment ceases, re-epithelialisation commences. Healing may occur within a few days or may be protracted and take a number of weeks to attain completion.

A surgical approach involves debridement of detached epidermis to remove potentially infected material followed by physiological wound closure using biosynthetic dressings, xenograft or allograft.40,47 This more aggressive approach can be considered following failure of conservative management, characterized by clinical deterioration, extension of epidermal detachment, local sepsis/sub-epidermal pus, delayed healing and wound conversion (the spontaneous progression of superficial skin loss into a deeper cutaneous defect).

Denuded dermis in SJS/TEN exudes serum and becomes coated with necrotic debris. The exposed dermis and haemorrhagic crust act as a substrate for microbial colonisation, initially by *Staphylococcus aureus* and later by gram-negative rods from the digestive flora, especially *Pseudomonas aeruginosa*.7 Cutaneous infection will impair re-epithelialisation and may lead to systemic sepsis, which is the commonest cause of death in SJS/TEN. Indiscriminate administration of prophylactic systemic antibiotics may increase skin colonisation, particularly with *Candida albicans,* thereforeantimicrobial therapy should only be instituted if there are clinical signs of infection.7 The SJS/TEN disease process may be accompanied by a fever which complicates detection of secondary sepsis; therefore patients should be monitored carefully for other signs of systemic infection such as confusion, hypotension, reduced urine output and reduced oxygen saturation.48 Cutaneous infection may be accompanied by an increase in skin pain. The detection of sepsis may also be indicated by a rise in CRP and neutrophilia. If a monoculture of organisms is detected on culture of swabs taken from multiple sites, which had previously showed mixed growth, this sign indicates that one particular strain of organism is becoming predominant and increases the likelihood of invasive infection.48 Consider activation of HSV in eroded or vesicular areas which are slow to heal, particularly in genital and oral sites.

**Recommendations: *(Strength of recommendation D (GPP); level of evidence 4*)**

**General principles applicable to all patients with SJS/TEN and in all settings:**

* Employ strict barrier nursing to reduce nosocomial infections.
* Careful handling of the patient’s skin and reduction of shearing forces will lessen the extent of epidermal detachment.
* Limit epidermal trauma by avoiding the use of sphygmomanometer cuffs, adhesive ECG leads, adhesive dressings, identification wrist tags.
* Take swabs for bacterial and candidal culture from three areas of lesional skin, particularly sloughy or crusted areas, on alternate days throughout the acute phase of SJS/TEN.
* Take viral swabs if herpes virus infection is suspected.
* Administer systemic antibiotics only if there are clinical signs of infection. The choice of systemic antibiotic should be guided by local microbiological advice.
* In patients with diarrhoea who are immobile consider a faecal management system to prevent faecal soiling of wounds.
* Pay strict attention to background and procedural pain / sedation requirements.

**Specific measures to manage necrotic and /or denuded areas of skin**

Skin management may involve a conservative and/or surgical approach based on the specialist multi-disciplinary team’s daily review of the individual needs of the patient

Institute a conservative approach in all patients as follows:

* Regularly cleanse wounds and intact skin by irrigating gently using warmed sterile water or saline or an antimicrobial such as chlorhexidine (1/5000).
* Apply a greasy emollient, such as 50% white soft paraffin with 50% liquid paraffin (50/50 WSP/LP), over the whole epidermis, including denuded areas; consider using aerosolized formulations to minimize shearing forces associated with topical applications. Avoid preparations containing sensitizers or irritants.
* Apply a topical antimicrobial agent to sloughy areas only. The choice of topical antibiotic should be guided by local microbiological advice. Consider Ag-containing products/dressings (use of Ag-containing products should be limited if extensive areas are being treated due to risk of absorption).
* The detached, lesional epidermis may be left *in situ* to act as a biological dressing. Blisters should bedecompressed by piercing and expression or aspiration of tissue fluid.
* Apply non-adherent dressings to denuded dermis (suitable dressings include Mepitel™ or Telfa™).
* A secondary foam or burn dressing should be used to collect exudate (suitable dressings include Exu-Dry®).

Consider transfer to a Burn Centre in patients with TEN (>30% BSA epidermal loss) and evidence of the following: clinical deterioration, extension of epidermal detachment, sub-epidermal pus, local sepsis, wound conversion and/or delayed healing. In a Burn Centre conservative measures may be supplemented with a surgical approach:

* Remove necrotic/loose infected epidermis and clean wounds using a topical antimicrobial agent (for example, betadine or chlorhexidine) under general anaesthetic.
* Consider debridement with VersajetTM.
* Physiological closure with Biobrane/ allograft /xenograft skin in patients with early presentation involving non infected and large confluent areas.

**8.3 What fluid replacement regimen should be followed in SJS/TEN?**

A major goal of supportive care in SJS/TEN is fluid resuscitation to prevent end-organ hypoperfusion and shock. Extensive epidermal detachment will result in large insensible, transcutaneous fluid losses, which is compounded by decreased oral intake due to disease involvement of the mouth. In burns patients the predicted volume of fluid replacement is proportional to the surface area of burn involvement: the Parkland formula is generally used, with fluid resuscitation in adults being commenced at 15% BSA involvement.49 In SJS/TEN, requirements are lower than those predicted by Parkland; over-aggressive fluid resuscitation may be associated with pulmonary, cutaneous and intestinal oedema. A study by Shiga *et al.* of 21 TEN patients with extensive epidermal loss recorded fluid requirements over the first 3 days of admission and estimated that replacement volumes can be determined by the following formula: 2 ml/kg body weight/% BSA epidermal detachment.50

**Recommendations: *(Strength of recommendation D; level of evidence 3)***

* Insert peripheral and central venous lines through non-lesional skin, whenever possible, and change peripheral venous cannulas every 48 hours, if possible.
* Monitor fluid balance carefully; catheterize if appropriate/necessary.
  + - Fluid replacement can be guided by urine output and other endpoint measurements (see below). Individualized fluid management should be adjusted on a daily basis
* When necessary, use continuous invasive haemodynamic monitoring through a central line to guide fluid resuscitation. Where estimation of fluid balance is challenging in severely affected patients, use central venous saturation and flow monitoring based on pulse contour analysis of arterial waveforms. Serial serum lactate measurements may also help to detect tissue hypoperfusion.
* After establishing adequate intravenous fluid replacement initially, oral administration of fluids should be progressively increased, if tolerated.

**8.4 What nutrition regimen should be followed in SJS/TEN?**

SJS/TEN is characterized by a hypermetabolic response with energy expenditure approximately twice the predicted resting value.51-53 Extensive epidermal detachment is also associated with loss of large amounts of albumin and protein from blister fluid. Therefore in SJS/TEN cases with significant areas of skin involvement a nutritional regimen must be initiated early to support metabolic disturbances, minimize protein losses and promote healing. As in other intensive care situations, enteral nutrition is preferable to parenteral nutrition to reduce peptic ulceration and limit translocation of gut bacteria. Since buccal mucositis in SJS/TEN often precludes normal oral intake, nasogastric feeding with a silicone tube should be instituted when necessary. General principles of intensive care nutrition are applicable and these are summarized in the European Society of Parenteral & Enteral Nutrition (ESPEN) guidelines.42,54

**Recommendations: *(Strength of recommendation C; level of evidence 3)***

* Provide continuous enteral nutrition throughout the acute phase of SJS/TEN, either by the oral route or via nasogastric feeding if the former is precluded by buccal mucositis.
* Deliver up to 20 to 25 kcal/kg/day during the early, catabolic phase of SJS/TEN. During the anabolic, recovery phase, the aim should be to provide between 25 to 30 kcal/kg/day.

**8.5 What analgesia is required in SJS/TEN?**

SJS/TEN is characterized by cutaneous pain, which is most severe at sites of epidermal detachment. There are no studies investigating different analgesic regimens in SJS/TEN. In the absence of disease-specific evidence, patient comfort should be ensured using the principles of the WHO analgesic ladder ([www.who.int/cancer/palliative/painladder/en/](http://www.who.int/cancer/palliative/painladder/en/)).55

Patients should receive adequate background simple analgesia to ensure comfort at rest, with the addition of opiates, as required, delivered enterally, or by patient-controlled analgesia (PCA), or via infusion. Involvement of the skin of the hands by SJS/TEN may limit the ability of the patient to operate a PCA device. If the patient is in moderate to severe pain, which is uncontrolled by simple analgesia, then an opiate-based regimen using morphine should be initiated. Careful monitoring of level of consciousness, respiratory rate and oxygen saturation is essential for safe delivery of opiate infusions. Additional analgesia is often needed to address increased pain associated with patient handling, re-positioning, dressing changes and physiotherapy.56 Intra-nasal diamorphine or sub-lingual fentanyl can be useful for more limited procedures.

Adjuvants, including GABA analogues, may have an opiate-sparing role. Topical anaesthesia of mucous membranes may facilitate placement of nasogastric tubes and urinary catheters.

**Recommendations: *(Strength of recommendation D (GPP); level of evidence 4)***

* Use a patient appropriate validated pain tool to assess pain in all conscious patients at least once a day.56 If the score is mild, pain control with regular paracetamol (acetaminophen) should be introduced, supplemented if required with oral opiate-based therapy such as codeine, or synthetic opiate such as tramadol. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided because of the potential for renal and gastric injury.
* If the pain score equates to moderate or severe pain then prescribe regular opiate-based analgesia (e.g. morphine or fentanyl) delivered enterally, or by patient-controlled analgesia (PCA), or via infusion. Intravenous opiates may be safely delivered in dedicated skin failure Burn Centres or ICUs, with appropriate nursing levels. In patients needing opiate-based analgesia, pain should be re-evaluated using the pain score on a 4-hourly basis and prior to any interventions. Involve the hospital acute pain team early.
* Procedures such as dressing changes and bathing may require supplementary analgesia. Entonox™ (50% nitrous oxide, 50% oxygen) may be useful for this purpose when the area of cutaneous involvement is small (< 10% BSA). Patients with significant areas of epidermal detachment will require additional pain relief for procedures. Practitioners trained in sedation techniques should deliver this in a safe monitored environment, such as an ICU, theatre or Burn Centre. Techniques to consider include target-controlled remifentanil infusions or bolus ketamine based analgo-sedation. Some patients may require general anaesthesia.

**8.6 What additional supportive medication is advisable in a patient with SJS/TEN?**

As in other critical care situations, patients with SJS/TEN are subject to stress-related gastric or duodenal ulceration and, if immobile, at risk of venous thromboembolism. Gastric protection with a proton pump inhibitor is recommended, in the minority in whom enteral nutrition cannot be established.57 Prophylactic anticoagulation with low molecular weight heparin is necessary, unless contraindicated.

Anaemia and leucopenia are common complications of the acute phase of SJS/TEN. Neutropenia will increase the risk of life-threatening sepsis and therefore administration of recombinant human G-CSF has been used to resist infectious complications.58 It has also been suggested that the use of G-CSF in SJS/TEN may be immunomodulatory and enhance re-epithelialisation.58

**Recommendations: *(Strength of recommendation C; level of evidence 3)***

* SJS/TEN patients who are immobile in bed should receive low molecular weight heparin as prophylactic anticoagulation against venous thromboembolism.
* During the acute phase of SJS/TEN, patients in whom enteral nutrition cannot be established may benefit from a proton pump inhibitor to protect against upper gastro-intestinal stress ulceration.
* SJS/TEN patients who are neutropenic may benefit from the administration of recombinant human G-CSF.

**9.0 TREATMENT OF EYE INVOLVEMENT IN SJS/TEN**

Acute ocular involvement in SJS/TEN usually occurs concurrently with skin disease, but may develop before or after the appearance of cutaneous signs. A longitudinal study by Gueudry *et al.* of 159 SJS/TEN patients demonstrated that 74% (117/159) suffered eye involvement during the acute phase of the illness.59 Inflammation of the mucosal surfaces of the eye and eyelids is accompanied by chemosis, conjunctivitis, pseudomembrane formation and corneal and conjunctival epithelial defects. Power *et al.* described a grading system for ocular SJS/TEN which describes the acute eye complications (see Table 5).60 Of the 159 patients in Gueudry *et al.*’s study 58% (92/159) had mild involvement, 8% (12/159) moderate and 8% (13/159) severe; in the remaining 26% (42/159) of patients there was either no acute eye involvement or no recording of acute eye features.59 Patients with TEN had more frequent, but not more severe, acute ocular involvement than patients with SJS. Sixty three percent (31/49) of those with acute ocular involvement went on to develop chronic complications.59 Yip *et al.* also used the Power *et al.* classification to assess the outcomes of 117 patients with SJS/TEN of whom 81 (69%) had acute ocular involvement.61 This was mild in 40%, moderate in 25% and severe in 4%. Forty-four patients had a minimum of 6 months of follow-up; 50% developed late complications, of which the commonest were severe dry eyes and trichiasis. There was no difference in the severity of acute eye involvement or late complications when SJS and TEN patients were compared. In addition the severity of the acute ocular disease was not a risk factor for late complications. The conclusions that can be drawn from these studies are that neither the severity of the systemic disease, nor the grade of the acute ocular disease, is predictive for late ocular complications. Because the latter may not become apparent until late after the acute episode, clinicians should be aware of this and make appropriate follow up arrangements. However, effective management of ocular inflammation in the acute stages of SJS/TEN, summarized in Table 5, will prevent or mitigate acute blinding, corneal complications and may reduce the severity of the chronic eye disease.

|  |  |
| --- | --- |
| Mild: | eyelid oedema |
| +/- mild conjunctival injection |
| +/- chemosis |
| Moderate: | membranous conjunctivitis |
| +/- corneal epithelial defects (>30% healing with medical therapy) |
| +/- corneal ulceration |
| +/- corneal infiltrates |
| Severe: | symblepharon formation |
| +/- non-healing corneal epithelial defects |
| +/- visual loss |
| +/- conjunctival fornix foreshortening |

**Table 5.** Classification of acute ocular involvement in SJS/TEN

Recently, a simplified system for grading ocular involvement has been published (Table 6).62 The grading is related both to predisposing factors for severe ocular complications and to poor late outcomes of visual disturbance and dry eye. It seems to be more predictive than the Power system.62,63

|  |  |
| --- | --- |
| **Grade** | **Acute Ocular Manifestations** |
| 0 (none) | No ocular involvement |
| 1 (mild) | Conjunctival hyperaemia |
| 2 (severe) | Either ocular surface epithelial defect  or pseudomembrane formation |
| 3 (very severe) | Both ocular surface epithelial defect  and pseudomembrane formation |

**Table 6.** Grading scores for acute ocular severity of SJS/TEN (table from Sotozono *et al.*)62

These long-term ocular manifestations, which constitute the most significant sequelae of SJS/TEN, include corneal and conjunctival scarring, severe dry eye due to aqueous tear deficiency, secondary to both cicatrisation of the lacrimal ductules and accessory lacrimal glands as well as meibomian gland dysfunction, mucin deficiency secondary to goblet cell destruction, distichiasis, entropion, trichiasis, and ocular surface failure.59 Patients with chronic eye involvement require lifelong management for dryness, conjunctival inflammation and ocular discomfort.

The management of the acute ophthalmological consequences of SJS/TEN demands the minimization of the destructive ocular surface and lid margin inflammation, the management and prevention of conjunctival adhesions, infection prophylaxis, and the prompt identification and management of the blinding complications of corneal exposure, ulceration and infection.

**9.1 In SJS/TEN, is topical therapy effective in treating ocular involvement?**

Local ocular measures are supportive and empirical. Ocular surface lubrication and conjunctival hygiene must be maintained throughout the acute illness. If an SJS/TEN patient on ICU or a Burn Centre is semi-conscious or unconscious, prevention of corneal exposure is essential.64,65 Compromise of corneal defences, or proven ocular infection, are indicators for the use of a topical antibiotic. Topical corticosteroids are commonly used to ameliorate conjunctival inflammation. A retrospective study of SJS/TEN cases compared 33 patients receiving ocular topical corticosteroid during the acute phase with 31 patients treated with lubricant alone;66 no information was given concerning the dose, length of treatment or type of topical corticosteroid used. Visual outcomes, assessed at an unspecified time after the acute episode, were significantly better in the group receiving topical corticosteroid compared with the lubricant group.66

**Recommendations: *(Strength of recommendation D (GPP); level of evidence 4)***

* The eyes should be examined by an ophthalmologist as a part of the initial assessment of a patient with SJS/TEN. Thereafter, daily ophthalmological review is necessary during the acute illness. A direct ophthalmoscope to provide illumination, magnification and a cobalt blue light source for fluorescein examination is useful.
* Two-hourly application of a lubricant (e.g. non-preserved hyaluronate or carmellose eye drops) should be started immediately and continued through the acute illness.
* Ocular hygiene, to remove inflammatory debris and break down conjunctival adhesions, must be carried out each day by an ophthalmologist or ophthalmic trained nurse, and can be performed using saline irrigation, a squint hook and forceps. Scissors may be needed when adhesions are well developed and cannot be removed with forceps alone. Blind sweeping of the fornices with a cotton bud or glass rod is not recommended and may potentially cause damage. The application of a topical local anaesthetic (e.g. proparacaine or tetracaine) is necessary prior to the procedure.
* In the unconscious patient, prevention of corneal exposure is essential to reduce the risk of ulceration and infection. Establishing a moisture chamber with polyethylene film should be used to maintain corneal epithelial integrity. On healthy eyelid skin paper tape can be used to affix the moisture chamber; care must be taken if there is sloughing of the eyelid skin. All ICUs and Burn Centres should have corneal exposure prophylaxis protocols in place.
* Broad-spectrum topical antibiotic prophylaxis is recommended by the authors in the presence of corneal fluorescein staining or frank ulceration, when microbial keratitis has been excluded. The choice of antibiotic should be guided by local knowledge of antimicrobial resistance patterns, which vary widely in different countries. In the UK a quinolone preparation is recommended, such as moxifloxacin or levofloxacin which has a wide range of activity against both Gram positive and negative organisms, used four times a day. Other UK experts recommend conjunctival cultures on admission and prophylaxis guided by the sensitivity results.
* For suspected corneal infection, which may manifest as corneal stromal loss in the absence of an infiltrate, culture guided treatment is mandatory following initial hourly use of broad spectrum topical antibiotic therapy, according to local protocols, and may be modified by microbial sensitivity results when these become available. Candida keratitis is relatively common in patients with surface disease so that cultures for both bacteria and fungus are required.
* The use of topical corticosteroid drops (e.g. non-preserved dexamethasone 0.1%), supervised by an ophthalmologist, may reduce ocular surface damage in the acute phase of SJS/TEN. Topical corticosteroids can mask the signs of corneal infection and should be used with caution in the presence of a corneal epithelial defect.
* Non-preserved (as opposed to preserved) topical eye drops are recommended; these are available in the UK for all the preparations mentioned above.

**9.2 In SJS/TEN, is systemic therapy effective in treating ocular involvement?**

Two studies have attempted to assess the efficacy of systemic therapy on ocular outcomes in SJS/TEN. A study by Araki *et al.* reported five patients with acute ocular SJS/TEN receiving pulsed intravenous methylprednisolone, followed by a tapering course of oral prednisolone;67 there was no control group. Treatment was started at a mean of 1.2 days after SJS/TEN onset. At 12 months, the best corrected visual acuity (VA) was 20/20 or better; there was slight discomfort in 10/10 eyes necessitating artificial tears; there was no evidence of epithelial defects, neovascularisation, opacification or keratinisation.67

In a retrospective case series from Yip *et al.* the ocular outcomes in eight TEN patients treated with intravenous immunoglobulin (IVIg) were compared with a group of eight historical controls, five of whom received oral prednisolone.68 The IVIg-treated group were all survivors (patients who died were excluded from study). A total of 25% (2/8) of patients had mild eye involvement, 50% (4/8) were moderately affected and 25% (2/8) had severe eye involvement. All patients received 2 g/kg IVIg over 2 days. 87.5% (7/8) received oral prednisolone prior to IVIg; 37.5% (3/8) received a tapering course of oral prednisolone after IVIg.68 The outcome measures were ocular complications and visual acuity at 6 weeks post-IVIg. There was no difference in severity of visually significant ocular complications between the IVIg and the control group.68

A further retrospective paper describes the effect of systemic immunomodulatory treatment on ocular outcomes in 43 patients from three centres treated with five systemic therapies: steroids (n=18), IVIG (n=5), steroids with IVIG (n=14), systemic pulse steroids (n=3) and supportive care only (n=3). This paper concluded that the grading system used62 had prognostic value for poor ocular outcomes but that their study could not demonstrate therapeutic benefit from the use of systemic immunomodulatory treatment to mitigate the ocular complications.63

When given in the acute phase of SJS/TEN, there is no robust evidence for the benefit of systemic corticosteroids or IVIg to improve ocular outcomes. Further studies are required to establish the role of either intervention.

**9.3 In SJS/TEN, is the use of amniotic membrane transplantation effective in treating ocular involvement?**

There are a number of published cases, and one case-controlled trial, reporting good ocular outcomes following amniotic membrane transplantation (AMT) during the acute phase of SJS/TEN.69-76 The suggested benefits of AMT include reduced inflammation, enhanced re-epithelialisation, reduction of scarring and less symblepharon formation.69-72 One case report of bilateral AMT suggests that early AMT may provide better outcomes than later application.77 Cryopreserved amniotic membrane (obtained from NHSBT Tissue services: 14 Estuary Banks, Estuary Commerce Park, Speke, Liverpool, L24 8RB) is now available in a large (5 x 5 cms) size, as well as smaller sizes. The large size is ideal for lining the entire ocular surface. AMT may be sutured onto the ocular surface, usually under general anaesthetic or deep sedation. The technique is described both by Muquit *et al.* (using a procedure also favoured by the authors, incorporating absorbable sutures that do not require a further anaesthetic for removal)78 and by Gregory *et al*. who recommend a similar procedure, but incorporating non-absorbable sutures and bolsters, which adds steps to the operation that may be unnecessary.70 Video is attached to both papers. For sutured AMT the risks are low, without complications reported in the available case series, and the procedure is not complex but time consuming. It takes about 90 minutes to perform on each eye, and is easier to carry out in an operating room under general anaesthesia although, as with most ophthalmological procedures, it can be carried out under local anaesthesia. After the procedure a symblepharon ring or conformer may be inserted. Symblepharon rings and conformers are available in the UK (Orbital Prosthetic Supplies, www.orbitalprosthetic.com): their use and sizing has been described.79 AMT performed at the bedside under topical anaesthesia has been published in four reports of eight SJS/TEN cases.72-75 In these patients, amniotic membrane was applied using a proprietary device and the tissue clipped into a plastic symblepharon ring (Prokera Bio-Tissue, Miami, USA).

It is possible to retain large sheets of amniotic membrane in the conjunctival sac using symblepharon rings or conformers only.80 The procedure can be performed at the bedside relatively easily. A large retrospective study comparing the results of AMT in 39 sutureless, and 36 sutured cases, demonstrated better outcomes in sutureless compared to sutured AMT.80

A retrospective study from one unit compared 17 SJS/TEN patients (33 eyes) receiving medical eye management with 13 patients (25 eyes) treated with AMT performed in the acute phase of the disease.76 Visual acuity assessed within 3 months of treatment demonstrated significantly better outcomes in the AMT group.76

**Recommendations: *(Strength of recommendation D; level of evidence 3)***

* For patients in whom ocular hygiene is impossible without general anaesthesia, and in those with extensive loss of ocular surface epithelia unresponsive to conservative measures, the use of amniotic membrane transplantation should be considered. It may improve outcomes if this procedure is carried out earlier rather than later in cases with severe ocular surface ulceration. Sutureless AMT using a symblepharon ring, and performed at the bedside, is a new, promising, low risk technique for delivering this therapy.

**10.0 TREATMENT OF MOUTH INVOLVEMENT IN SJS/TEN**

Oral involvement in SJS/TEN is characterized by painful mucosal erythema with subsequent blistering and ulceration. Similar involvement of the vermillion of the lips progresses to haemorrhagic sloughing with the development of dark adherent crusts. The tongue and palate are frequently affected while in severe cases mucosal involvement may extend to the oropharynx, larynx, respiratory tract and oesophagus. Drinking and eating are usually severely compromised by oral involvement in acute SJS/TEN. If tolerated, ingested foods need to be soft, moist and low in acidity. However, fluids usually need to be given intravenously and nutrition supplied via a soft, fine-bore naso-gastric tube (see section 8.4).

A long-term complication of acute oral involvement is labial and intra-oral scarring which may restrict mouth opening and cause difficulty with eating or speaking.81 Sicca syndrome, caused by damage to minor salivary glands, develops as a chronic problem in up to 40% of patients.82

**10.1 In SJS/TEN, is topical therapy effective in treating oral involvement?**

Local measures for treating oral involvement in acute SJS/TEN are supportive and empirical. Along with regular examination of the mouth and lips, attention should be given to regular emollients, topical analgesia and topical antiseptics. In an uncontrolled series of patients with a variety of blistering conditions affecting the mouth, including SJS/TEN, topical corticosteroids were shown to reduce oral inflammation.83 Topical corticosteroids are widely prescribed in oral SJS/TEN, but there is limited directly applicable evidence for their use.

**Recommendations: *(Strength of recommendation D (GPP); level of evidence 4)***

* The mouth should be examined as a part of the initial assessment of a patient with SJS/TEN. Thereafter, daily oral review is necessary during the acute illness.
* Apply white soft paraffin ointment to the lips immediately, and then every two hours throughout the acute illness. Protect ulcerated mucosal surfaces with a mucoprotectant mouthwash, used three times a day (e.g. Gelclair®). Clean the mouth daily with warm saline mouthwashes or an oral sponge, sweeping the sponge gently in the labial and buccal sulci to reduce the risk of fibrotic scars.
* Use an anti-inflammatory oral rinse or spray containing benzydamine hydrochloride every 3 hours, particularly before eating. If pain is inadequately controlled with benzydamine, then a topical anaesthetic preparation, e.g. viscous lidocaine 2%, 15 ml per application, may be used as an alternative. Cocaine mouthwashes 2% to 5% can be used for severe oral discomfort three times a day.
* Use an antiseptic oral rinse twice a day to reduce bacterial colonization of the mucosa. Agents available include 1.5% hydrogen peroxide mouthwash (e.g. Peroxyl® mouthwash, 10 ml twice a day) or 0.2% chlorhexidine digluconate mouthwash (e.g. Corsodyl® mouthwash, 10 ml twice a day). Diluting 0.2% chlorhexidine mouthwash by up to 50% will reduce the soreness which can accompany this treatment.
* Oral and lip swabs should be taken regularly if bacterial or candidal secondary infection is suspected. Candidal infection should be treated with nystatin oral suspension 100,000 units four times a day for 1 week, or miconazole oral gel (e.g. Daktarin® oral gel) 5 to 10 ml held in the mouth after food four times a day for 1 week. Slow healing of the oral mucosa may reflect secondary infection by, or reactivation of, HSV.
* Consider using a topical corticosteroid four times a day (e.g. betamethasone sodium phosphate 0.5 mg in 10 ml water as a 3-minute rinse-and-spit preparation). A more potent preparation, clobetasol propionate 0.05%, mixed in equal amounts with Orabase®, can be applied directly to the sulci, labial or buccal mucosae daily during the acute phase.

**10.2 In SJS/TEN, is systemic therapy effective in treating oral involvement?**

There are no controlled trials of systemic corticosteroid in the management of mouth involvement in SJS/TEN, however, steroids are commonly used by oral physicians in severe EM major. In a series comprising eight EM major cases and four cases of SJS, patients were treated with fluocinolone or prednisolone or methylprednisolone in a variety of doses for 5 to 7 days during the acute illness.84 Oral assessment revealed a complete remission of buccal lesions in all patients 7 to 10 days after onset of systemic corticosteroid treatment.84 Nonetheless, there is currently insufficient evidence to recommend systemic corticosteroids for the treatment of the oral manifestations of acute SJS/TEN. There are no published studies of oral outcomes in acute SJS/TEN treated with systemic ciclosporin or IVIg.

**11.0 TREATMENT OF UROGENITAL INVOLVEMENT IN SJS/TEN**

Involvement of the urogenital tract in SJS/TEN is characterized by mucosal erythema, blistering and erosions. During the acute phase pain is prominent and urinary dysfunction (dysuria or retention) is common. Secondary infection by bacteria or candida is a frequent complication of urogenital involvement. HSV activation may also occur. Erosions of the genital mucosae may persist for many weeks after the acute phase has resolved, ultimately healing with scarring.85,86 In the long term, serious morbidity can ensue in the form of strictures and stenosis of the urethra, phimosis in males and vaginal synechiae in females, with resultant urinary and sexual dysfunction.87

**11.1 In SJS/TEN, is topical therapy effective in treating urogenital involvement?**

Local measures for treating urogenital involvement in acute SJS/TEN are supportive and empirical. Along with regular examination of the urogenital tract, attention should be given to regular emollient, appropriate dressings and topical anti-microbial treatment. Topical corticosteroids may be useful to reduce urogenital inflammation.88,89

**Recommendations: *(Strength of recommendation D (GPP); level of evidence 4)***

* Examine the urogenital tract as a part of the initial assessment of a patient with SJS/TEN. In women, early assessment by a vulval specialist is recommended for consideration of dilators to prevent vaginal synechiae. Speculum examination needs to be undertaken with plastic speculums so that all vaginal walls can be fully assessed. Uncircumcised male patients should be checked for preputial retractability. Thereafter, daily documented urogenital review is necessary during the acute illness.
* Apply white soft paraffin ointment to the urogenital skin and mucosae immediately and thereafter 4 hourly through the acute illness.
* Use Mepitel™ dressings to eroded areas in the vulva and vagina to reduce pain and prevent adhesions. A dilator or tampon wrapped in Mepitel™ should be inserted into the vagina to prevent formation of synechiae.
* Consider applying a potent topical corticosteroid ointment once a day to the involved, non-eroded, urogenital surfaces.
* Catheterize all patients to prevent strictures forming in the urethra.

**11.2 In SJS/TEN, is systemic therapy effective in treating urogenital involvement?**

There are no published studies of urogenital outcomes in acute SJS/TEN treated with systemic corticosteroids, ciclosporin or IVIg.

**12.0 TREATMENT OF AIRWAY INVOLVEMENT IN SJS/TEN**

Pulmonary complications are an under-appreciated manifestation of SJS/TEN, and may be a marker of disease severity and mortality. Respiratory tract involvement does not seem to correlate with the extent of epidermal detachment.

A single-centre, prospective study characterized airway involvement in SJS/TEN into three groups based on whether hypoxaemia and respiratory symptoms were present, and the time-course of the development of hypoxaemia.90 Patients without hypoxaemia during the acute phase (group 1) suffered no pulmonary complications or sequelae and had low mortality.90 One-quarter of patients presented with early pulmonary manifestations (group 2) characterized by dyspnoea and an increased respiratory rate - chest radiographs were typically normal on admission, with later diffuse pulmonary infiltrates.90 Bronchial hypersecretion occurred in 70% of these patients, and fibre-optic bronchoscopy revealed a pattern of diffuse loss of bronchial epithelium in the proximal airways, with evolving epithelial detachment caused by epithelial necrosis. There was no evidence of airway infection in this group, and normal bronchial mucosa began to recover at the same time as skin recovery in survivors. Mechanical ventilation was required in 90% of cases, and a high mortality rate (70%) was reported. In patients with bronchial epithelial necrolysis airway sloughing may occur, and can cause sudden airway obstruction and death.91 A small percentage of patients with early pulmonary manifestations go on to develop chronic respiratory problems, which include bronchiolitis obliterans, bronchiectasis and chronic bronchitis. The prognosis is poor, with a mortality rate of approximately 40%.92 Delayed pulmonary manifestations (group 3) occurred in 19% of cases and consisted of a heterogeneous group of conditions including atelectasis, bacterial pneumonia and fluid overload.90 Biopsy confirmed the absence of pulmonary epithelial detachment in these patients; there was no requirement for ventilation in this group, and all patients recovered.90

**Recommendations: *(Strength of recommendation D (GPP); level of evidence 4)***

* Respiratory symptoms and hypoxaemia on admission should prompt urgent discussion with an intensivist and rapid transfer to the ICU or Burn Centre, since deterioration requiring mechanical ventilation is likely. Relatives should be counselled as to the prognostic significance of this development.
* Fibre-optic bronchoscopy should be undertaken to identify bronchial involvement, evaluate prognosis and investigate the presence of pneumonitis by bacterial sampling. Bronchoscopy may have a role in preventing atelectasis and airway obstruction by allowing the mechanical removal of sloughed bronchial epithelium.
* Patients with on-going respiratory symptoms should be closely monitored with pulmonary function testing and high-resolution CT scanning.

**13.0 ACTIVE THERAPY IN SJS/TEN**

Currently, no active therapeutic regimen with unequivocal benefit exists for SJS/TEN. Only one randomized controlled trial has been conducted in TEN: the anti-TNF agent thalidomide was compared to placebo, however the study was discontinued prematurely because of an excess of deaths in the thalidomide treatment group.93

The immunological basis for SJS/TEN has lead physicians to prescribe immunomodulating drugs, several of which have been studied in uncontrolled series. In this guideline, active interventions were assessed if studies recruited at least eight SJS/TEN patients into the treatment group. Of all active interventions (excluding thalidomide) only three drugs fulfilled the inclusion criteria; IVIg, systemic corticosteroid and ciclosporin.

**13.1 Is treatment with intravenous immunoglobulin effective in SJS/TEN?**

Evidence for possible efficacy of IVIg in SJS/TEN came from a study indicating a role for Fas-Fas ligand (Fas-FasL) interaction in TEN keratinocyte apoptosis.12This study demonstrated that high concentrations of normal immunoglobulin inhibited Fas-FasL interaction and apoptosis through anti-Fas activity. The authors then reported an uncontrolled, prospective open trial of ten TEN patients treated with IVIg, none of whom died.12 Since Viard *et al.*’s report in 1998, a further 14 studies of IVIg treatment in SJS/TEN have met the inclusion criteria for assessment (data summarized in Table 7).28,34,46,94-104 Of the 15 studies identified, ten are retrospective cohort studies and five are prospective. Pooling the results yields a total of 302 SJS/TEN patients receiving IVIg, however, one study96 contained patients reported in previously published series, thus the total number of patients is lower. In all studies the primary outcome measure is mortality. In a systemic review and meta-analysis, published in 2012 by Huang *et al.* (all studies of at least eight SJS/TEN patients receiving IVIg) a pooled estimate of mortality risk was determined, comparing IVIg and supportive care in patients with TEN and SJS-TEN overlap.105 Statistical analysis was also performed on the raw data to compare the clinical differences between high-dose and low-dose treatment in adult patients and between paediatric and adult patients treated with IVIg. Overall mortality rate of 221 patients with TEN and SJS-TEN overlap (patients with SJS were not included) treated with IVIg was 19.9%. The pooled odds ratio (OR) for mortality from six observational controlled studies comparing IVIg and supportive care was 1.00 [95% confidence interval (CI) 0.58-1.75; P=0.99].105 Paediatric patients treated with IVIg had significantly lower mortality than adults (0% versus 21.6%, respectively; P=0.001). Adults treated with high-dose IVIg exhibited significantly lower mortality than those treated with low-dose IVIg (18.9% versus 50%, respectively; P=0.022); however, multivariate logistic regression model adjustment indicated that IVIg dose does not correlate with mortality (high-dose versus low-dose: OR 0.494; 95% CI 0.106-2.300; P=0.369).105 These findings should however, be interpreted with caution given the major methodological limitations of the original cohorts. Since the publication of Huang *et al.*’s meta-analysis, a further study by Firoz *et al.*, which included 23 TEN patients treated with IVIg, demonstrated no improved survival in subjects receiving IVIg versus supportive care alone.104 In 2013 Lee *et al.* published a retrospective analysis of 64 patients with SJS-TEN overlap or TEN treated with IVIg at a single specialised referral centre in Singapore.106 The mortality in their patients, when compared to predicted outcome from SCORTEN, showed no benefit from IVIg.106 In addition, when stratified according to dosage, there was no mortality difference between patients who received high-dose (>3 g/kg) versus low-dose (<3 g/kg) IVIg.106

**13.2 Is treatment with systemic corticosteroid effective in SJS/TEN?**

Corticosteroids have been used in the management of SJS/TEN for many years. Proponents emphasize the importance of high-dose corticosteroid given early in the disease course to inhibit inflammation; opponents suggest that systemic corticosteroids increase the risk of sepsis. Ten published studies of corticosteroid treatment in SJS/TEN meet the inclusion criteria for assessment: all are case series, none are randomized controlled trials and most are retrospective.28-30,34,107-111 Retrospective analysis of the EuroSCAR data indicated a lower mortality in German patients (but not French patients) treated with corticosteroids compared to controls receiving supportive care alone.28 Two studies have investigated the effects of pulsed intravenous high dose corticosteroids.107,112 In the study by Kardaun *et al.*, 12 patients received 100mg or 1.5 mg/kg of IV dexamethasone for 3 days and were reported to have a decreased mortality compared with SCORTEN.112 Hirahara *et al.* presented a series of eight SJS/TEN patients who received 1000 mg of IV methylprednisolone on 3 consecutive days, followed by either a tapering course of oral prednisolone, or a further 2 days of half-dose IV methylprednisolone.112 No patients died despite a SCORTEN-predicted mortality of 1.6.112 Data from the corticosteroid studies are summarized in Table 8. Sources of potential bias are indicated in the table.

**13.3 Is treatment with ciclosporin effective in SJS/TEN?**

Effective inhibition of lymphocyte function identifies ciclosporin as a drug with theoretical efficacy in SJS/TEN. Four cohort studies of ciclosporin treatment in SJS/TEN meet the inclusion criteria for assessment (summarized in Table 9).113-116 A study by Valeyrie-Allanore *et al.* from the dermatology ITU in Creteil, Paris demonstrated that in 29 SJS/TEN patients ciclosporin given at a dose of 3 mg/kg/day for 10 days, and thereafter tapered, was effective. There were no deaths, despite a SCORTEN predicted mortality of 2.75/29.114 Singh *et al.* reported 11 SJS/TEN patients treated with ciclosporin 3 mg/kg/day for 7 days, and then tapered over a further 7 days. This group was compared to six historical SJS/TEN controls treated with systemic corticosteroids.115 There was a significantly enhanced speed of epithelialisation and reduced length of hospital stay in the ciclosporin group.115 Comparison of SCORTEN-predicted mortality demonstrated a benefit of ciclosporin over corticosteroids.115 Kirchhof *et al.* published a retrospective review from a single centre of 64 SJS/TEN patients receiving either ciclosporin or IVIg (doses of each varied).116 Analysis of predicted SCORTEN mortality compared with actual mortality indicated a relative mortality benefit for the use of ciclosporin (standardised mortality ratio [SMR] 0.43) versus IVIg (SMR 1.43).116 Data from the ciclosporin studies are summarised in Table 9. Sources of potential bias are indicated in the table.

**13.4 Other treatments used in the management of SJS/TEN**

Other therapies have been tried in SJS/TEN, but studies contain small numbers of patients and are, generally, uncontrolled. Plasmapheresis has been used in SJS/TEN which is refractory to treatment; reports suggest that this therapeutic modality may provide a rapid benefit.117,118 The bioregeneratory and immunomodulatory properties of G-CSF, have led some to claim efficacy (that transcends the management of leucopaenia) in the active treatment of TEN by arresting the hypersensitivity and stimulating re-epithelialisation.58 More recently there has been interest in a therapeutic role for TNF-alpha inhibitors. Paradisi *et al.* reported a series of ten SJS/TEN patients treated with a single 50 mg subcutaneous dose of etanercept. There was no control group. All patients responded with a mean re-epithelialisation time of 8.5 days. None of the patients died, despite a mean SCORTEN-predicted mortality rate of ~50%.119

**13.5 Evidence synthesis**

The GDG found interpretation of the reviewed studies challenging given major ascertainment bias in reported cohorts, low numbers of patients, variation in the timing and nature of intervention, case mix and setting, and quality of supportive care. The GDG did not consider any of the data presented of sufficient quality or consistency to make specific recommendations either for or against the use of active interventions and highlighted the need for future research (See Section 16). It was noted that there is a lack of consensus even amongst clinicians with experience in managing SJS/TEN, with, for example, strong advocates for use and avoidance of IVIg.

Withdrawal of culprit drug and meticulous attention to high quality, multidisciplinary supportive care is the priority.

**Recommendations: *(Strength of recommendation D; level of evidence 4)***

* There is no conclusive evidence to demonstrate the benefit of any one intervention over conservative management, nor evidence to demonstrate harm from IVIg, systemic corticosteroids or ciclosporin in the context of SJS/TEN. The GDG considers that, ideally, such interventions should be practised under the supervision of a specialist skin failure MDT in the context of a clinical study or a case registry.

**14.0 DISCHARGE AND FOLLOW-UP**

As the patient recovers from the muco-cutaneous and systemic manifestations of acute SJS/TEN, preparations can be made for discharge. Before leaving the hospital, information on the culprit drug should be relayed to the patient. The drug allergy should be documented in the patient’s notes (or electronic patient record) and communicated to all physicians involved in the patient’s care. Recent NICE guidelines highlight the importance of ensuring adequate documentation and information sharing regarding drug allergy.120 An adverse drug reaction should be reported to the pharmacovigilance authorities (the MHRA in the UK, [www.mhra.gov.uk](http://www.mhra.gov.uk)).

At discharge an explanatory letter outlining the disorder should be sent to the patient’s GP. The letter should state the culprit medication, outline the potential complications of SJS/TEN, and specify the patient’s follow-up plan (see Appendix 2: Specimen discharge letter). NICE guidance suggests that severe non‑immediate cutaneous reactions are referred to a specialist drug allergy service for expert review, which in the context of SJS/TEN is likely to be a dermatology unit with appropriate sub-specialty interest.120

Fatigue and lethargy is a major problem for several weeks following discharge; the patient, his/her relations and employers need to be aware of this. Usually a period of convalescence following hospital discharge is necessary. Psychological problems, including depression, are also common during this time.121 Chronic complications of SJS/TEN may develop weeks to months after the acute episode and are associated with significant morbidity and reduced quality of life. Ocular damage, arising from corneal scarring, is the most disabling complication and may develop at a variable period after the acute disease.122 Long-term sequelae can involve other organs and survivors need monitoring for potential complications in multiple systems.

**Recommendations: *(Strength of recommendation D(GPP); level of evidence 4)***

* Give the patient written information about the drug(s) to avoid. The name(s) of any related medication(s) which may cross-react with the culprit should also be given to the patient. Educate the patient about the necessity to avoid the triggering drug(s).
* At discharge, refer the patient to local social services, when appropriate to arrange a needs assessment for support. If necessary, refer to the occupation therapy department.
* Access support from SJS Awareness UK http://www.sjsawareness.org.uk/ or appropriate national SJS/TEN support group.
* Encourage the patient to wear a MedicAlert bracelet or amulet bearing the name of the culprit drug.
* The drug allergy should be documented in the patient’s notes. All doctors involved in the patient’s care, especially the GP, should be informed about the drug allergy episode and the culprit.
* Warn the patient to avoid over-the-counter medications where precise constituents are unclear.
* Report episode of drug-induced SJS/TEN to the national pharmacovigilance authorities (the MHRA’s Yellow Card Scheme in the UK, [w](http://www.yellowcard.gov.uk)ww.yellowcard.mhra.gov.uk).
* If the patient had eye involvement during the acute phase, organize an outpatient clinic appointment with an ophthalmologist within a few weeks of discharge.
* Organize an outpatient clinic appointment within a few weeks of discharge. Patients need to be monitored for complications in skin, mouth, urogenital tract, respiratory and gastro-intestinal systems. Psychological evaluation and support should be considered.

**Table 7**: Summary of IVIg studies in SJS/TEN

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Setting** | **Design** | **Patient numbers** | **Intervention:**  **IVIg dose** | **Outcome:**  **mortality** | **Comparator** | **Reported**  **benefit** | **Level of evidence[[1]](#footnote-1)** | **Additional notes** |
|  |  |  |  |
| **Viard**  **1998**12 | Multiple  centres | Prospective  Case series  Non-controlled | TEN (10) | 0.2-0.75 g/kg/d for 4 days | 0/10 (0%) | Not applicable | Effective | 3 | Variable IVIg dosing |
| **Stella**  **2001**94 | Single burns unit | Prospective  Case series  Non-controlled | SJS (1)  Overlap SJS/TEN (7)  TEN (1) | 0.6-0.7 g/kg/d for 4 days | 1/9 (11%) | Not applicable | Effective | 3 |  |
| **Bachot**  **2003**97 | Single dermatology  HDU | Prospective  case series with SCORTEN-predicted mortality as comparator | SJS (9)  Overlap  SJS/TEN (5)  TEN (20) | 2 g/kg given over 2 days | 11/34 (32%) | SCORTEN-predicted mortality  8.2/34 (24%) | Ineffective | 3 |  |
| **Campione**  **2003**98 | Single dermatology unit | Retrospective case series with SCORTEN-predicted mortality as comparator | TEN (10) | 2 g/kg given over 5 days | 1/10 (10%) | SCORTEN-predicted mortality  3.5/10 (35%) | Effective | 3 |  |
| **Prins**  **2003**96 | Multiple centres | Retrospective  Case series (including previously reported cases, from 3 other studies)  Non-controlled | Overlap SJS/TEN (7)  TEN (41) | Mean 0.7 g/kg/d for 4 days | 6/48 (13%) | Not applicable | Effective | 3 | Duplicated cases from Viard *et al*  1998,12 Campione *et al* 200398 and Trent *et al* 200395 |
| **Trent**  **2003**95 | Single dermatology  unit | Retrospective case series with SCORTEN-predicted mortality as comparator | Overlap SJS/TEN (6)  TEN (10) | 1 g/kg/d for 4 days (n=15)  0.4 g/kg/d for 4 days (n=1) | 1/16 (6%) | SCORTEN-predicted mortality  5.81/16 (36%) | Effective | 3 |  |
| **Al-Mutairi 2004**99 | Single dermatology unit | Retrospective, non-controlled | TEN (12) | 0.5-1 g/4-5 days | 0/11 (0%) | Not applicable | Effective | 3 |  |
| **Brown**  **2004**100 | Single Burns unit | Retrospective,  case-control | TEN (24) | 0.4 g/kg for 4 days | 10/24 (42%) | 6/21 (29%) mortality in steroid-treated controls | Ineffective | 2- |  |
| **Shortt**  **2004**101 | Single Burns unit | Retrospective  Case-control | Overlap SJS/TEN (16) | Mean dose 0.7 +/- 0.2 g/kg daily for 4 +/- 1 days | 4/16 (25%) | 6/16 (38%) mortality in historic controls | Equivocal | 2- |  |
| **Kim 2005**34 | Dermatology unit | Retrospective case series with SCORTEN-predicted mortality as comparator | TEN (14) | IVIg: 1.6 – 2.0 g/kg | 1/14 (7%) | SCORTEN-predicted mortality: 2.4/14 (17%) | Effective | 3 |  |
| **Tan 2005**102 | Dermatology unit | Retrospective  Case series  Non-controlled | Overlap SJS/TEN (4) TEN (8) | 2 g/kg over 2 days in 10 patients; 1.5 g/kg over 2 days in 2 patients  9/12 patients had corticosteroid prior to IVIg. | 1/12 (8%) | No comparator group | Effective | 3 | Cases validated but histopathological evidence in only 4/12 cases  Co-treatment with corticosteroid |
| **Gravante 2007**103 | Burns unit | Retrospective  Case series | SJS (1)  TEN (16) | 0.4 g/kg daily for 5 days | 7/17 | No comparator group or SCORTEN-predicted mortality given | Effective | 3 |  |
| **Stella 2007**46 | Burns unit | Retrospective case-control series  Control group – supportive care only | IVIg group:  SJS (2)  Overlap  SJS/TEN (16)  TEN (5)  Control group:  TEN (8) | 0.7 g/kg daily for 4 days + methylprednisolone 250 mg qds for 2 days | 6/23 (26%) | SCORTEN-predicted mortality 8.2/23 (36%) | Effective | 3 | This series included 9 cases published in Stella *et al.* 2001.94  Control group  TBSA involvement significantly lower in IVIg group compared to controls. |
| **Schneck 2008**28 | Burns and dermatology units | Retrospective  Case-controlled | SJS (9)  Overlap  SJS/TEN (11)  TEN (15) | Mean dose 1.9 g/kg over 1 – 7 days | 12/35 (34%) | Mortality for supportive care alone 22/87 (25%) | Ineffective | 2- | Well-validated cases.  Study may have included cases published in Bachot *et al.* 2003.97  Heterogeneous care settings |
| **Firoz 2012**104 | Single burns unit | Prospective  Case-controlled  SCORTEN-based comparison | TEN (23) | 4 g/kg over 3 days | No significant difference in survival between IVIg group and control | Supportive care only (n=51) | Ineffective | 2- |  |
| **Lee 2013106** | Single specialized centre | Retrospective SCORTEN-based comparison | Overlap SJS/TEN (28) TEN (36) | Mean dose 2.4 g/kg over 4 days | 20/64 (31%) | SCORTEN-predicted mortality 18.22/64 (28%) | Ineffective | 2- | No mortality difference when stratified according to high-dose or low-dose IVIg |
| **Aihara 2015123** | Multiple dermatology centres | Prospective  Case series  No comparator group | SJS (5)  TEN (3) | 400 mg/kg/d IVIg for 5 consecutive days in conjunction with systemic corticosteroid therapy (variable dose) | 0/8 (0%)  7/8 patients classed as ‘responders’ according to a severity-of-illness score designed by the authors | None | Effective | 3 | Co-treatment of all patients with corticosteroid - variable dosing.  Only 8/41 cases included in the final report – reporting bias |

**Table 8**: Summary of corticosteroid studies in SJS/TEN

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Setting** | **Design** | **Patient numbers** | **Intervention** | **Outcome (mortality)** | **Comparator** | **Reported benefit** | **Level of evidence1** | **Additional notes** |
| **Murphy 1997**111 | Single  Burn Centre | Retrospective  Case series  Non-controlled | TEN (12) | Highly variable doses received, no details re specific dosing | 8/12 | Not applicable | No comment made by authors | 3 | Timing, duration and dose of corticosteroid therapy highly variable. |
| **Schulz 2000**29 | Single  Burn Centre | Retrospective  Case series  Non-controlled | TEN (34) | No details about corticosteroid dosing | 13/34 | Not applicable | Ineffective | 3 | No evidence of case validation  No details regarding steroid dosing. |
| **Tripathi 2000**108 | Single dermatology centre | Retrospective  Case series  Non-controlled | SJS (13) | Methylprednisolone 160 – 240 mg/day – tapered when clinical response seen (no mean duration given) | 1/13 | Not applicable | No comment | 3 | No evidence of case validation |
| **Ducic 2002**30 | Single Burn Centre | Retrospective  Case series  Non-controlled | TEN (29) | No information about dosage provided | 13/29 | Not applicable | No comment made by authors | 3 | No evidence of case validation.  TEN diagnosis based on ≥20% BSA detachment as opposed to 30%, therefore some cases may be overlap.  No information about corticosteroid dosing. |
| **Kim 2005**34 | Single dermatology centre | Retrospective.  Case series  Non-controlled | TEN (21) | Methylpred 250 – 1000 mg/day, later switched to oral prednisolone | 6/21 mortality | SCORTEN predicated mortality 5.97 | Ineffective | 3 | Some attempt to validate cases.  Variable doses of steroid used, no details about tapering. |
| **Kardaun 2007**107 | Single dermatology centre | Retrospective  Case series  Non-controlled | SJS (1)  Overlap SJS/TEN (4)  TEN (7) | First 4 patients: IV dexamethasome 100 mg od x 3 days plus 500mg cyclophosphamide  Subsequent patients: 1.5mg/kg IV dexamethasone x 3 days | 1/12 | SCORTEN predicted mortality: 4/12 | Effective | 3 | Case validation unclear.  Change of treatment protocol during series |
| **Schneck 2008**28 | Multiple centres in Germany and France. | Retrospective  Case series  Non-controlled | SJS (57)  Overlap SJS/TEN (44)  TEN (18) | Max steroids dose 250 mg prednisolone equivalent (Interquartile range 100-500 mg).  Given for median 4 days (2 – 12 days). | 21/119 | Mortality expressed as odds ratio: Corticosteroids compared to supportive care alone OR 0.4 (0.1-1.7) in France, and 0.3 (0.1-1.1) in Germany. Overall: 0.4 (0.2 – 0.9) | Ineffective (on multivariate analysis) | 2- | Robust case validatoin  Steroid group had less severe disease than IVIg group. |
| **Yang 2009**109 | Single dermatology centre | Retrospective  Case series  Non-controlled | SJS (10) and TEN (35) in corticosteroid arm (n=45)  SJS (8) and TEN (12) in IVIg/corticosteroid arm (n=20) | 1 – 1.5 mg/kg/day methylprednisolone or equivalent (details not given)  IVIg 0.4 g/kg/day for 5 days | 10/45 (10 TEN) in corticosteroid group  3/20 (2 TEN and 1 SJS) in IVIg/corticosteroid group | SCORTEN predicted mortality 8.63 in corticosteroid group; 3.51 in IVIg/corticosteroid group | Corticosteroid alone ineffective, IVIg/corticosteroid may confer benefit (non-significant difference) | 2- | Case validation unclear  Insufficient detail on corticosteroid dosing |
| **Chen 2010**110 | Single dermatology centre | Retrospective.  Case series  Non-controlled | SJS (43) and TEN (15) in corticosteroid only arm (n=58)  SJS (9) and TEN (15) in IVIg/corticosteroid group (n=24) | Hydorcortisone 100 – 700 mg/day or methylprednisolone 40 – 80 mg/day. (Cumulative dose equivalent to prednisolone 10 – 25 mg/kg/day for 7 – 14 days)  IVIg mean dose 2.7 ±1.5 g/kg over 3 – 15 days | 2/58 in corticosteroid group  3/24 in IVIg/corticosteroid group | SCORTEN predicted mortality 4.2 in corticosteroid group; 5.3 in IVIg/corticosteroid group | Effective | 2- | Results suggesting benefit did not reach statistical significance. Patients in IVIg/corticosteroid group had higher TBSA involvement at baseline |
| **Hirahara 2013112** | Single dermatology centre | Retrospective Case series Non-controlled | SJS (3)Overlap SJS/TEN (2)TEN (3) | 1000 mg IV methylpred for 3 days | 0/8 | SCORTEN-predicted mortality 1.6/8 (20%) | Effective | 3 | Subsequent doses of corticosteroid varied according to response. |

See Appendix 1

**Table 9**: Summary of ciclosporin studies in SJS/TEN

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Setting** | **Design** | **Patient numbers** | **Intervention** | **Outcome: mortality** | **Comparator** | **Reported benefit** | **Level of evidence1** | **Additional notes** |
| **Arvalo 2000**113 | Burns unit | Case-Control study (historic controls) | TEN (11) | Cases treated with 3 mg/kg CyA for 14 days, tapered by 10 mg/day for a further 2 weeks, then stopped | 0/11 | 3/6 in cyclophosphamide group  Cyclophosphamide 150 mg bd and methylprednisolone – variable doses (> or = 1 mg/kg/day | Yes | 3 | No evidence of case validation (though all cases have histopathological confirmation).  Possible overestimation of BSA involvement  Co-treatment with steroid and ciclophosphamide in control group at variable doses |
| **Valeyrie-Allanore 2010**114 | Dermatological intensive care unit | Case Series with SCORTEN-based predicted mortality as comparator | SJS (10), Overlap SJS/TEN (12), TEN (7) | CyA 3 mg/kg for 10 days tapered over 1 month. | 0/29 | SCORTEN-predicted mortality = 2.75 | Yes | 2 | Good validation.  No control group  Consistent dosing among patients |
| **Singh 2013115** | Dermatology unit | Case control study (historic controls) | SJS (5),  Overlap SJS/TEN (3)  TEN (3) | CyA 3 mg/kg/day for 7 days, and tapered for 7 days. | 0/11 | SCORTEN-predicted mortality in control group treated with corticosteroid | Yes | 3 | No evidence of case validation |
| **Kirchhof 2014116** | Dermatology unit | Retrospective series: CyA versus IVIg | Overlap SJS/TEN (64) | Various doses of CyA and IVIg | CyA SMR 0.43  IVIg SMR 1.43 | CyA treated group compared to IVIg treated group | Yes | 3 | No evidence of case validation  No control group |

See Appendix 1

**15.0 DRUG HYPERSENSITIVITY TESTS IN SJS/TEN**

Once a diagnosis of drug-induced SJS/TEN has been made, investigations may be helpful in confirming or identifying the culprit medication. Since T cell-mediated mechanisms predominate in SJS/TEN, assays for drug-specific IgE-mediated immediate reactions (i.e. skin prick testing and specific IgE testing) are of no value. Appropriate tests are those which identify delayed type IV hypersensitivity reactions, most notably drug patch testing and *in vitro* assays, such as drug-induced T cell proliferation (lymphocyte transformation tests) and drug-induced lymphocyte cytokine production. Oral provocation studies are not ethical in SJS/TEN because of a risk of life-threatening reactions. Although a lesser risk, induction of severe reactions has been recorded with patch testing.

**15.1 What is the evidence that patch tests can identify a culprit drug in SJS/TEN?**

Reviews have commented on the value of patch testing in drug allergy and have suggested explanations for the variable sensitivity and specificity of this assay in different reaction patterns and with different drugs.124 A study by Wolkenstein *et al.* patch tested 22 cases of SJS/TEN (series n=59) and found only 9% (2/22) of the cases to be positive.125 Another study by Lin *et al.* demonstrated positive patch tests to carbamazepine in 62.5% (10/16) of cases of carbamazepine-induced SJS/TEN, compared with 0% (0/10) controls.126 In this study cross-reactivity to other aromatic anticonvulsant drugs was observed. A recent French multi-centre study reported 17 patients with SJS/TEN where positive patch tests were identified in 24% (4/17) of cases, but in this series patch testing showed positive reactions in 0% (0/5) of cases of carbamazepine-induced SJS/TEN.127

**15.2 What is the evidence that *in vitro* tests can identify a culprit drug in SJS/TEN?**

The method of isolation of peripheral blood mononuclear cells (PBMC) followed by *in vitro* challenge with the putative causal drug has been widely studied in the context of drug hypersensitivity testing. Although these assays involve the culture of PBMC with the drug in question, it is generally accepted that the responding cells are T lymphocytes.

1. ***Lymphocyte transformation tests (LTT; lymphocyte proliferation assay)***

Lymphocyte proliferation as measured by uptake of 3H-thymidine in dividing cells is widely referred to as the LTT. However, variations in standard methodology mean that comparative interpretation is difficult. Overall, the number of reports specifically characterising the value of LTT for SJS/TEN is low. Studies have reported positive LTT responses in 100% (4/4) of SJS cases to a variety of culprit drugs,128 and 75% (3/4) of SJS cases, again triggered by a range of medicines.129 However, neither of these reports compared drug-LTT assays in a control population. A study by Kano *et al.* showed that in two cases of SJS, LTT results were positive in the acute phase of the reaction but weakened over 2 months.130 A report by Tang *et al.* suggested that LTT was not of value for the investigation of lamotrigine-induced SJS/TEN since only 21.4% (3/14) cases showed a positive result.131

A study by Roujeau *et al.* reported 11 cases tested with LTT within 1 month of recovery from TEN.132 Although 44% of cases showed positive LTTs to the culprit drug, control groups also showed a similar frequency of positive drug LTT assays.132 The authors concluded that the assay is not useful in cases of TEN. However, other series have shown positive results in only 15% and 0% (0/18) of controls.133,134 In Polak *et al.*’s series, 56% (5/9) of EM/SJS/TEN cases demonstrated positive LTT’s, in the context of a low false-positive rate of 4.9%,135 whilst other series showed the LTT to be positive in only 27% (4/15) of cases.134 Lymphocyte proliferation measured by other techniques such as the carboxyfluorescein succinimidyl ester (CFSE) dilution assay has not been widely examined in SJS/TEN. A recent report has suggested that blockade of inhibitory molecules to T cell proliferation during the LTT assay (with anti-CTLA4, and anti-PDL1), may increase positivity from 32% to 50%.136

1. ***Lymphocyte function assays***

Drug-induced lymphocyte production of cytokines or other mediators measured by ELISA, ELISpot or intracellular fluorescence, has the advantage of utilising a shorter assay time and does not require the use of radioisotopes. Furthermore, it does not rely on lymphocyte proliferation which is likely to be more susceptible to direct drug toxicity *in vitro.* However, these assays are technically more challenging and require more complicated equipment.

Published reports have suggested the value of cytokine assays incorporating IFN-γ, IL-2, IL-4, IL-5, IL-13, IL-17, granzyme B, sFasL, granulysin and others to investigate drug hypersensitivity *in vitro*.135,137-142In Polak *et al*.’s study, IFN-γ drug ELISpot assays tested at a median of 19 days (IQR ±11 days) after the onset of the reaction were shown to identify causal drugs in 78% (7/9) of cases of EM/SJS/TEN.135 IL-4 ELISpot was less sensitive and detected only 50% (4/8) of cases.135 A series of nine cases of SJS/TEN reported that 100% of cases had positive IFN-γ ELISpot assays when tested after a median of 12 months (IQR ±3 months) and 66.6% (6/9) of cases also showed drug-induced sFasL production.142 Detection of drug-induced IFN-γ has also been demonstrated in a recent series of 15 cases of SJS/TEN and in this series, measurements of granzyme B and IL-5 release following drug exposure were also significantly higher in patients as compared to controls.134

Due to ethical considerations, currently no diagnostic tests for SJS/TEN have been validated by deliberate re-exposure challenge testing to the suspected culprit drug. Consequently, true sensitivity is not known and the possibility of false positive and false negative results exists. However, it is generally accepted that re-exposure to a drug showing a positive result (from patch or blood tests) is likely to represent a significant risk of re-initiation of SJS/TEN. Diagnostic testing is not likely to be of benefit in cases where a culprit drug can be imputed with a high level of confidence from clinical grounds (for example where exposure was to only one medication). Furthermore, in cases where strict avoidance of possible culprit drugs and related compounds is of little consequence to the individual, the risk of false negative testing is likely to outweigh the benefits of the test.  In cases where medication avoidance is detrimental to the individual or where accidental exposure is possible, further investigation may be warranted. Patch testing is generally safe but of low diagnostic value for the investigation of SJS/TEN causality. Patch testing specificity and sensitivity are drug-dependent. Although LTT is of uncertain diagnostic value, lymphocyte drug-induced IFN-γ assays are of value for the investigation of SJS/TEN causality. However, evidence from several groups suggests that combination assays show increased sensitivity over one assay alone. The use of in vitro tests by clinicians will be determined by the availability of the relevant assays in specialist laboratories. Diagnostic testing should be interpreted by physicians experienced in the management of SJS/TEN who are familiar with the test system. It is to be emphasised that the tests described here have not been evaluated as tools for the diagnosis of SJS/TEN when the clinical picture is not typical.

**Recommendations: *(Strength of recommendation D(GPP); level of evidence 4)***

* Routine drug hypersensitivity testing is not recommended following an episode of SJS/TEN.
* Seek specialist advice on formal drug hypersensitivity testing where the culprit drug cannot be imputed with confidence and where medication avoidance is detrimental to the individual or where accidental exposure is possible (also, see follow-up recommendations above).120 Current evidence supports the use of lymphocyte drug-induced IFN-γ assay as part of the investigative work-up.

**16.0 FUTURE DIRECTIONS**

Improving the management of patients with SJS/TEN requires attention to both the processes of care delivery as well as to individual components of the therapeutic regimen. It has been suggested that SJS/TEN patient management should be carried out in a small number of regional centres, each equipped with appropriate intensive care facilities and specialist expertise.143 In this way, standardized care could be delivered to provide high quality care with improved clinical outcomes. Establishing a national network of SJS/TEN centres would enable the implementation of appropriate governance structures, including: case registration on a national database; supra-regional case conferences for case validation and standardisation of care; regular audits against defined standards of care; opportunities for training and continuing professional development for the network members.

Future research into the management of the acute phase of SJS/TEN needs to answer a number of important questions:

* What constitutes optimal supportive care?
* What, if any, are the optimum active, systemic therapies?
* What are the optimal investigations to identify the culprit drug in SJS/TEN?

**17.0 RECOMMENDED AUDIT POINTS**

For each patient with SJS/TEN in the last 5 years:

1. Has the patient had a SCORTEN performed on admission?
2. Has drug causality assessment been undertaken within the first 24 hours of admission?
3. Has the patient been seen by an ophthalmologist within 24 hours of admission? Have daily ocular assessments been made throughout the acute phase?
4. Has an initial assessment of mouth and urogenital tract involvement been undertaken within the first 24 hours of admission? Have daily oral and urogenital assessments been made throughout the acute phase?
5. At discharge, has:
   1. contact been made with the patient’s GP?
   2. the patient been counselled about future avoidance of the culprit drug(s)?
   3. a MedicAlert bracelet/amulet been requested?

**18.0 SUMMARY**

**(see full manuscript for details of evidence)**

|  |  |
| --- | --- |
| **Initial assessment on presentation** | * Take a detailed history from the patient and/or relatives * Perform a full physical examination, including baseline body weight and record the vital signs, including oxygen saturation * Order a set of investigations: FBC, U&E, LFT, glucose, magnesium, phosphate, bicarbonate, mycoplasma serology, CXR, skin biopsy and baseline body weight * Initiate a primary management plan:  1. establish peripheral venous access 2. if patient cannot maintain adequate nutrition orally, insert a nasogastric tube and institute nasogastric feeding 3. insert a urinary catheter if urogenital involvement is causing significant dysuria/retention   **(Strength of recommendation D (GPP))** |
| **Determination of drug causality** | * Identify causative agent and withdraw immediately   **(Strength of recommendation D)** |
| **Prognostic scoring** | * Calculate SCORTEN within the first 24 hours   **(Strength of recommendation C)** |
| **Care setting** | * A multi-disciplinary team should be convened, co-ordinated by a specialist in skin failure, usually dermatology and/or plastic surgery, and including clinicians from intensive care, ophthalmology and skin-care nursing * Patients with greater than 10% BSA epidermal loss should be admitted without delay to a Burn Centre or ICU with experience of treating patients with SJS/TEN and facilities to manage the logistics of extensive skin loss wound care * Patients must be barrier-nursed in a side room controlled for humidity, on a pressure-relieving mattress with the ambient temperature raised to between 25° and 28°C   **(Strength of recommendation D (GPP))** |
| **Skin management regimen 1**  ***Applicable to all patients in all settings*** | * Employ strict barrier nursing to reduce nosocomial infections * Take swabs for bacterial and candidal culture from three areas of lesional skin, particularly sloughy or crusted areas, on alternate days throughout the acute phase * Administer systemic antibiotics only if there are clinical signs of infection   **(Strength of recommendation D (GPP))** |
| **Skin management regimen 2**  ***This may involve a conservative and/or surgical approach based on the specialist multi-disciplinary team’s daily review of the individual needs of the patient*** | **Institute a conservative approach in all patients as follows:**   * Regularly cleanse wounds and intact skin by irrigating gently using warmed sterile water, saline or an antimicrobial such as chlorhexidine (1/5000) * Apply a greasy emollient, such as 50% white soft paraffin with 50% liquid paraffin (50/50 WSP/LP), over the whole epidermis, including denuded areas * Apply a topical antimicrobial agent to sloughy areas only (choice should be guided by local microbiological advice). Consider Ag-containing products/dressings. * The detached, lesional epidermis may be left *in situ* to act as a biological dressing. Blisters should bedecompressed by piercing and expression or aspiration of tissue fluid. * Apply non-adherent dressings to denuded dermis (suitable dressings include Mepitel™ or Telfa™). * A secondary foam or burn dressing should be used to collect exudate (suitable dressings include Exu-Dry®).   **Consider transfer to a Burn Centre in patients with TEN (>30% BSA epidermal loss) and evidence of the following: clinical deterioration, extension of epidermal detachment, sub-epidermal pus, local sepsis, wound conversion and/or delayed healing. In a Burn Centre conservative measures may be supplemented with a surgical approach.**   * Remove necrotic/loose infected epidermis and clean wounds using a topical antimicrobial agent (e.g. betadine or chlorhexidine) under general anaesthetic * Consider debridment with VersajetTM * Physiological closure with Biobrane/ allograft /xenograft skin in patients with early presentation involving non infected and large confluent areas   **(Strength of recommendation D (GPP))** |
| **Fluid replacement regimen** | * Site venous lines through non-lesional skin, whenever possible, and change peripheral venous cannulas every 48 hours * Monitor fluid balance carefully: catheterize if appropriate/necessary * Establish adequate intravenous fluid replacement initially. Fluid replacement can be guided by urine output and other endpoint measurements. Individualized fluid management should be adjusted on a daily basis. * With improvement of SJS/TEN mouth involvement, oral administration of fluids should be progressively increased   **(Strength of recommendation D)** |
| **Nutrition regimen** | * Provide continuous enteral nutrition throughout the acute phase * Deliver up to 20 to 25 kcal/kg/day during the early, catabolic phase and 25 to 30 kcal/kg/day during the anabolic, recovery phase   **(Strength of recommendation C)** |
| **Analgesia** | * Use a patient appropriate validated pain tool to assess pain in all conscious patients at least once a day * Patients should receive adequate analgesia to ensure comfort at rest, with the addition of supplementary opiates, as required * Additional analgesia may be needed to address increased pain associated with patient handling, re-positioning and dressing changes   **(Strength of recommendation D (GPP))** |
| **Supportive Therapeutic Measures** | * Immobile patients should receive low molecular weight heparin * Patients in whom enteral nutrition cannot be established should receive a proton pump inhibitor to reduce the risk of stress-related gastro-intestinal ulceration * Neutropenic patients may benefit from recombinant human G-CSF   **(Strength of recommendation C)** |
| **Treatment of eye involvement** | * Daily ophthalmological review is necessary during the acute illness * Apply an ocular lubricant (e.g. non-preserved hyaluronate or carmellose eye drops) every two hours through the acute illness * Ocular hygiene must be carried out each day by an ophthalmologist or ophthalmic-trained nurse * Application of topical corticosteroid drops (e.g. non-preserved dexamethasone 0.1% twice a day) may reduce ocular surface damage * Administer a broad-spectrum topical antibiotic as prophylaxis (e.g. moxifloxacin drops four times a day) in the presence of corneal fluorescein staining or frank ulceration * In the unconscious patient, prevention of corneal exposure is essential   **(Strength of recommendation D (GPP))** |
| **Treatment of mouth involvement** | * Daily oral review is necessary during the acute illness * Apply white soft paraffin ointment to the lips every two hours through the acute illness * Clean the mouth daily with warm saline mouthwashes or an oral sponge * Use an anti-inflammatory oral rinse or spray containing benzydamine hydrochloride every three hours, particularly before eating * Use an anti-septic oral rinse containing chlorhexidine twice a day * Use a potent topical corticosteroid mouthwash (e.g. betamethasone sodium phosphate) four times a day   **(Strength of recommendation D (GPP))** |
| **Treatment of urogenital involvement** | * Daily urogenital review is necessary during the acute illness * Apply white soft paraffin ointment to the urogenital skin and mucosae every four hours through the acute illness * Use a potent topical corticosteroid ointment once a day to the involved, but non-eroded, surfaces * Use a silicone dressing (e.g. MepitelTM) to eroded areas   **(Strength of recommendation D (GPP))** |
| **Treatment of airway involvement** | * Respiratory symptoms and hypoxaemia on admission should prompt early discussion with an intensivist and rapid transfer to an ICU or Burn Centre, where fibre-optic bronchoscopy should be undertaken   **(Strength of recommendation D (GPP))** |
| **Active therapy** | * If active therapy is instituted it should be given, ideally, under the supervision of a specialist skin failure MDT in the context of clinical research and/or case registry   **(Strength of recommendation D)** |
| **Discharge and follow-up** | * Give the patient written information about drug(s) to avoid * Encourage the patient to wear a MedicAlert bracelet * Drug allergy should be documented in the patient’s notes; all doctors involved in the patient’s care should be informed * Report the episode to the national pharmacovigilance authorities * Organize an out-patient clinic appointment, and if required an ophthalmology out-patient appointment, within a few weeks of discharge * Refer for review to unit with appropriate sub-speciality interest   **(Strength of recommendation D (GPP))** |
| **Diagnostic testing** | * Routine drug hypersensitivity testing is not recommended following an episode of SJS/TEN. * Seek specialist advice on hypersensitivity testing where:  1. the culprit drug is not known **or** 2. medication avoidance is detrimental to the individual **or** 3. accidental exposure is possible   **(Strength of recommendation D (GPP))** |

**SUPPORTING INFORMATION**

Additional supporting information including the search strategy may be found in the online version of this article.

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**APPENDIX 1**

**Levels of evidence**

|  |  |
| --- | --- |
| Level of evidence | Type of evidence |
| 1++ | High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias |
| 1+ | Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias |
| 1- | Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias\* |
| 2++ | High-quality systematic reviews of case-control or cohort studies  High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal |
| 2+ | Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal |
| 2- | Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal\* |
| 3 | Non-analytical studies (for example, case reports, case series) |
| 4 | Expert opinion, formal consensus |

\*Studies with a level of evidence ‘-’ should not be used as a basis for making a recommendation.

**Strength of recommendation**

|  |  |
| --- | --- |
| Class | Evidence |
| A | At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population, or  A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results  Evidence drawn from a NICE technology appraisal |
| B | A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results, or  Extrapolated evidence from studies rated as 1++ or 1+ |
| C | A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results, or  Extrapolated evidence from studies rated as 2++ |
| D | Evidence level 3 or 4, or  Extrapolated evidence from studies rated as 2+, or  Formal consensus |
| D (GPP) | A good practice point (GPP) is a recommendation for best practice based on the experience of the guideline development group |

RCT: randomized controlled trial; NICE: National Institute for Health and Clinical Excellence.

**APPENDIX 2.** **Discharge letter**

Dear Colleague,

Re: PATIENT’S NAME

Your patient was recently admitted to hospital following an episode of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). SJS/TEN is a rare, severe muco-cutaneous reaction, usually to drugs, characterised by blistering and epithelial sloughing of skin and mucous membranes. During the acute phase, patients are extremely ill, often requiring admission to an ICU or to a Burn Centre. The chronic phase of SJS/TEN is characterised by symptoms which develop insidiously over the weeks and months following presentation and usually persist after discharge from hospital. The most common sequelae are:

* Fatigue, especially in the initial weeks and months after discharge
* Eye complications, including dryness, pain, photophobia, corneal scarring and visual impairment
* Skin dyspigmentation (both hyper- and hypopigmentation)
* Loss of nails (sometimes with dystrophic regrowth)
* Urogenital problems, including dryness and complications from scarring
* Mouth problems, including dryness, dental caries and complications from scarring
* Post-traumatic stress disorder, including nightmares, anxiety and depression
* Other complications include bronchiectasis and other sequelae of lung involvement; stenosis of the gastrointestinal tract; loss of muscle mass

Your vigilance in monitoring for these complications is vital; many of the long-term outcomes, particularly ocular disorders, can be improved by early recognition and prompt intervention. In the event of any of the above sequelae please contact our department and we will refer the patient to the appropriate specialist.

SJS/TEN is most often caused by a medication. In the case of your patient the cause of SJS/TEN has been identified as ……………... . It is essential that your patient is not prescribed ……………... , or drugs of the same class. We have informed him/her about which medication(s) to avoid. We would appreciate if you could order a MedicAlert bracelet or amulet identifying the culprit medication(s) above and indicating the reaction he/she suffered (SJS/TEN). Some patients develop a reluctance to take new medicines, however, recurrences are extremely rare and are almost always due to a repeat exposure to the offending drug or another in the same class.

*If appropriate:* In approximately 15% of SJS/TEN cases no drug can be implicated.

Please contact the department if you wish to discuss your patient’s illness, or for further information about SJS/TEN.

Yours sincerely,

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Fig 1. Atypical targets. On the palm of this patient with SJS/TEN there are numerous circular lesions; most are characterised by a dark red centre surrounded by a pink ring, In areas, the lesions are confluent.

Fig 2. Purpuric macules. This patient with SJS/TEN developed numerous dark red, flat lesions on the torso and back. Over a few days the lesions had joined to produce large areas of dusky erythema.

Fig 3. Scattered lesions. Discrete lesions in SJS/TEN may be disseminated widely over the torso and limbs. In this case, the patient developed numerous dusky and blistering lesions on the neck, chest and abdomen. She also has severe mouth involvement and is being fed through a naso-gastric tube.

Fig 4. Involvement of plantar skin. Involvement of palms and soles in SJS/TEN can be prominent and, as at other sites, may blister.

Fig 5. Confluent erythema. Confluent erythema is covering the back; there are small eroded areas of epidermal detachment on the upper back.

Fig 6. Skin shearing. The epidermis within an area of lesional skin on this man’s thigh has peeled away following minimal trauma.

Fig 7. Blisters. Numerous large, flaccid blisters developed on the back of this woman who had SJS-TEN overlap. In her case there was epidermal detachment of 20% of her body surface area (BSA).

Fig 8. Epidermal loss. Extensive necrolysis results in the detachment of sheets of epidermis and exposure of large areas of denuded dermis. This patient with TEN had epidermal detachment of 60% BSA.

Fig 9. Eye involvement. Upper panel: early in the acute phase of SJS/TEN there is a purulent kerato-conjunctivitis and eyelid oedema. Lower panel: the same patient 3 days later, there is persistent ocular inflammation and involvement of eyelid skin.

Fig 10. Mouth involvement. Upper panel: a severe exudative and erosive cheilitis is typical. Lower panel: erosions may occur at any buccal site within the mouth including, as in this case, the palate.

Fig 11. Genital involvement. Involvement of the urethral meatus is visible, along with lesions elsewhere on the penis and confluent involvement of the scrotum. In this patient, the mucositis also affected the distal urethra.

Fig 12. Histopathology of SJS/TEN. There are multiple apoptotic keratinocytes throughout the full-thickness of the epidermis, and a subepidermal split forming a bulla. There is a perivascular lymphocytic infiltrate within the dermis.

Fig 13. Body map schematics of skin involvement in SJS/TEN. 13 A: extent of skin erythema (in pink) = 65% body surface area (BSA); extent of epidermal detachment (in red) = 10% BSA. 13 B: extent of erythema (in pink) = 90% BSA; extent of epidermal detachment (in red) = 45% BSA.

Fig 14. SJS/TEN Pathway of Care

1. [↑](#footnote-ref-1)