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British Association of Dermatologists guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in children and young people 2018

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NICE has accredited the process used by the British Association of Dermatologists to produce clinical guidelines. The renewed accreditation is valid until 31 May 2021 and applies to guidance produced using the process described in Updated guidance for writing a British Association of Dermatologists clinical guidance – the adoption of the GRADE methodology 2016. The original accreditation term began on 12 May 2010. More information on accreditation can be viewed at 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 children (0-12) and young people (13-17) during the acute phase of the disease. The document aims to:

- offer an appraisal of all relevant literature up to July 2018, focusing on any key developments
- address important, practical clinical questions relating to the primary guideline objective
- provide guideline recommendations and if appropriate research recommendations
- discuss areas of uncertainty, potential developments and future directions

These guidelines aim to provide recommendations on the diagnosis and management of paediatric SJS/TEN, to inform clinical decision-making and, when justified by evidence, to standardize practice. There is currently widely divergent practice amongst different specialities and healthcare settings, and limited information on outcomes. This document should be sufficient to assist clinicians of all relevant specialities in the management of children (≤12 years old) and young people (<18 years old) 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. The guideline is presented as a detailed review with highlighted recommendations for practical use in primary care and in secondary care clinics, in addition to an updated Patient Information Leaflet (PIL; available on the BAD website, www.bad.org.uk/for-the-public/patient-information-leaflets).

1.1 Exclusions

The guideline does not cover adults (≥18 years old); a separate BAD guideline for the management of SJS/TEN in adults has been published.[1]

2.0 METHODOLOGY

This set of guidelines has been developed using the BAD's recommended methodology[2] with reference to the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument [www.agreetrust.org][3] and the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[4] Recommendations were developed for implementation in the UK National Health Service (NHS).

The guideline development group (GDG), which consisted of consultant paediatric dermatologists, consultant dermatologists, a consultant plastic and reconstructive surgeon, a consultant paediatric anaesthetist, a consultant ophthalmologist with a specialist interest in paediatric ophthalmology, a dermatology specialist registrar, a paediatric dermatology clinical nurse specialist, patient/carer representatives and a technical team (consisting of a guideline research fellow and project manager providing methodological and technical support), established several clinical questions pertinent to the scope of the guideline and a set of outcome measures of importance to patients, ranked according to the GRADE methodology (see section 2.1).

A systematic literature search of PubMed, MEDLINE, EMBASE, Cochrane and AMED databases was conducted to identify key articles on SJS/TEN up to July 2018; search terms and strategies are detailed in the supplementary information (Appendix I). Additional references relevant to the topic were also isolated from citations in reviewed literature. Evidence from included studies was graded according to the GRADE system (high, moderate, low or very low quality). Recommendations are based on evidence drawn from systematic reviews of the literature pertaining to the clinical questions identified; the summary of findings with narrative findings tables (Appendices C, D & E), tables Linking the Evidence To the Recommendations (LETR) (Appendix B), PRISMA flow diagram (Appendix F), and list of excluded studies (Appendix G), are detailed in the supplementary information. The strength of recommendation is expressed by the wording and symbols as shown in Table 1.

Strength	Wording	Symbols	Definition
Strong recommendation *for* the use of an intervention	"Offer" *(or similar, e.g. "Use", "Provide", "Take", "Investigate", etc.)*	↑↑	Benefits of the intervention outweigh the risks; most patients would choose the intervention whilst only a small proportion would not; for clinicians, most of their patients would receive the intervention; for policy makers, it would be a useful performance indicator.

Weak recommendation *for* the use of an intervention	"Consider"	↑	Risks and benefits of the intervention are finely balanced; most patients would choose the intervention but many would not; clinicians would need to consider the pros and cons for the patient in the context of the evidence; for policy makers, it would be a poor performance indicator where variability in practice is expected.
No recommendation		ʘ	Insufficient evidence to support any recommendation.
Strong recommendation *against* the use of an intervention	"Do not offer"	↓↓	Risks of the intervention outweigh the benefits; most patients would *not* choose the intervention whilst only a small proportion would; for clinicians, most of their patients would *not* receive the intervention.

Table 1: Strength of recommendation ratings

2.1 Clinical Questions and Outcomes

The GDG established a clinical question pertinent to the scope of the guideline (See supplementary information Appendix A for full review protocol). The GDG also established a set of outcome measures of importance to patients (treatment), which were agreed by the patient representatives, ranked according to the GRADE methodology,[5] data on which are extracted from included studies (see Appendices C, D & E).

Review question	In children and young people with Stevens-Johnson syndrome/toxic epidermal necrolysis what are the clinical effectiveness of interventions, including active therapies, compared with each other?
Population	All children (0-12 years old) and young people (13-17 years old) with Stevens-Johnson syndrome/toxic epidermal necrolysis
Interventions *(acute phase and long-term)*	• Topicals – corticosteroids, calcineurin inhibitors, ciclosporin, antibiotics • Systemics – corticosteroids, IVIg, ciclosporin, G-CSF, LMW heparin, biologic therapy • Debridement • Others – proton pump inhibitors, plasmapheresis, amniotic membrane • Management of infection (causative and secondary) • Psychological interventions
Comparisons	• Topicals – corticosteroids, calcineurin inhibitors, ciclosporin, antibiotics • Systemics – corticosteroids, IVIg, ciclosporin, G-CSF, LMW heparin, biologic therapy

	• Debridement • Others – proton pump inhibitors, plasmapheresis, amniotic membrane • Management of infection (causative and secondary) • Psychological interventions

Outcomes	***Critical***
	• Survivorship/Survival (**9**)
	• Internal organ dysfunction and support – PELOD, modified SOFA or MODS score (**8**)
	• No residual impairment (7)
	  o Eyes – ocular surface disease, eyelid management, trichiasis, meibomian (**7**)
	  o Skin – scarring, dyschromia, dyspigmentation (**7**)
	  o Genital – phimosis, adhesion, meatal scarring (**7**)
	• Quality of life and psychosocial well-being – cDLQI and other measures, time to recovery, time to return to school/work (**7**)
	Important
	• Duration of hospitalization (**6**)
	• Ventilated days (**6**)
	• Recurrence (**6**)

3.0 SUMMARY OF RECOMMENDATIONS

There were no randomized controlled trials (RCTs) to support the following guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in children and young people. The following recommendations and ratings were agreed upon unanimously by the core members of the GDG and patient representatives. For further information on the wording used for recommendations and strength of recommendation ratings see section 2. The GDG is aware of the lack of high-quality evidence for these recommendations, therefore strong recommendations with an asterisk (*) are based on available evidence and/or consensus within the GDG and specialist experience. Most of the recommendations are derived from the adult version of the guideline, with appropriate modifications, and are ordered to follow the patient journey. Good practice point (GPP) recommendations are derived from informal consensus.

All the recommendations listed below apply to children and young people with SJS/TEN. Specific recommendations for any sub-population are indicated.

Initial assessment on presentation

R1 (↑↑) Take* a detailed history from children/young people with SJS/TEN and their parents/carers with specific reference to the following:

- 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)
- date when the rash first appeared and document progression of the eruption
- symptoms indicating involvement of the genital tract including pain and urinary retention
- symptoms indicating involvement of the respiratory tract: cough, dyspnoea, bronchial hypersecretion, haemoptysis
- symptoms indicating bowel involvement: diarrhoea, abdominal distension
- date when patient developed the first symptom or sign of the disorder, e.g. sore throat, rash, skin pain, sore eyes/mouth
- previous or on-going medical problems; specifically, history of previous drug reactions, recurrent herpes simplex virus (HSV) infections, chest infections, diagnosis and treatment for malignancy and/or stem cell transplant

Diagnosis and causality

R2 (↑↑) Exclude* the differential diagnosis staphylococcal scalded skin syndrome (SSSS), by clinical assessment of mucosae (not involved in SSSS) and skin biopsy if any diagnostic uncertainty

R3 (↑↑) Investigate* potential infectious aetiology in all patients and identify children/young people with specific clinical phenotypes more likely to be caused by respiratory infections (e.g. clinically predominant mucositis with limited skin involvement: respiratory infection-induced rash and mucositis 'RIRMS')

R4 (↑↑) Investigate* the triggering role of HSV, mycoplasma or chlamydia infections. Discuss with infectious diseases team, depending on clinical presentation and results of infectious screen; consider targeted antibiotics as appropriate (e.g. mycoplasma – azithromycin).

R5 (↑↑) Record* all medicines taken and vaccinations received over the preceding 2 months, including over-the-counter and complementary/alternative therapies:

- the date treatments were initiated
- the date of dose escalation, where appropriate
- the date when drugs were stopped
- brand switch or medication errors

ALDEN is an online tool that can be used to predict likely causality of a drug reaction.

R6 (↑↑) Immediately discontinue* any potential culprit drug causing SJS/TEN

Clinical assessment: Prognostic indicators

R7 (↑↑) Identify* high-risk children/young people, e.g. those with likely drug trigger and underlying diseases associated with a worse prognosis, e.g. malignancy and previous stem cell transplant

R8 (↑) Consider calculating SCORTEN to give a prognostic indicator

R9 (↑↑) Perform* a full physical examination:

- baseline body weight
- record vital signs and measure oxygen saturation with a pulse oximeter
- assess patency of airway and immediately involve anaesthetic staff if any concerns regarding need for intubation (see R11 & R13)
- examine respiratory system to exclude pneumonia/respiratory compromise
- examine skin: look for target lesions, particularly atypical targets, purpuric macules, blisters, and areas of epidermal detachment
- examine mouth, eyes and genitalia (including perianal skin) looking for mucositis, blisters and erosions
- record the extent of erythema and extent of epidermal detachment separately on a body map (Figure 1); for each parameter estimate the percentage of BSA involved using the Lund and Browder (L&B) chart

R10 (↑↑) Within 24 hours of diagnosis, arrange* an examination of the eyes by an ophthalmologist experienced in ocular surface diseases in children/young people (ideally with experience in SJS/TEN)

Stabilisation

R11 (↑↑) Assess* airway by a paediatric anaesthetist or paediatric intensivist and consider intubation if clinical signs support this, especially if a transfer is planned. Ensure immediate availability of appropriate equipment for a difficult intubation.

R12 (↑) Consider involvement of ear, nose and throat team for further airway assessment

R13 (↑↑) Initiate* early discussion with a paediatric intensivist if respiratory symptoms are present, with rapid transfer to a paediatric intensive care unit (PICU) where fibre-optic bronchoscopy *could* be considered

R14 (↑↑) Establish* peripheral venous access; where possible, insert the cannula through non-lesional skin; commence appropriate intravenous fluid resuscitation if clinically indicated; beware of hyponatraemia. Record accurately fluid intake and output and balance

R15 (↑↑) Record* weight and repeat at frequent intervals as required clinically (no less than weekly)

R16 (↑↑) Ascertain* if the child/young person can maintain adequate hydration and nutrition orally; if this is not possible, insert a nasogastric tube and institute nasogastric feeding immediately

R17 (↑↑) Insert* a urinary catheter if urogenital involvement is causing significant dysuria or retention; a urinary catheter should also be placed in those with significant skin loss to permit accurate output monitoring and assist with fluid replacement

R18 (↑↑) Involve* relevant specialists experienced in the management of SJS/TEN (see Care setting)

Investigations

R19 (↑↑) Order* the following set of investigations:

- full blood count (FBC); C-reactive protein (CRP); urea and electrolytes (U&E); liver function tests (LFT) and coagulation studies; glucose; magnesium; phosphate; bicarbonate; base excess; lactate
    - infection screening as clinically relevant and following discussion with infectious diseases team; relevant tests include mycoplasma and chlamydia serology, skin swabs for HSV and varicella zoster virus (VZV), and chest X-ray (CXR)
- bacterial swabs from lesional skin for culture and sensitivity
- conjunctival swabs for bacteria, chlamydia, HSV (PCR) and adenovirus (PCR)
- photographs of the skin to show type of lesion and extent of involvement
- skin biopsy from lesional skin, just adjacent to a blister, sent for routine histopathology; a second biopsy taken from peri-lesional skin should be sent unfixed for direct immunofluorescence if required to exclude an immunobullous disorder (N.B. If SSSS is clinically typical then no biopsy is required. However, if SSSS is considered but with diagnostic uncertainty, perform a shave biopsy of blister roof for frozen section as it is less invasive than a full-thickness skin biopsy)

Care setting

R20 (↑↑) Convene* a local multi-disciplinary team (MDT) led by a specialist in skin failure: dermatology and/or burns specialist, and include clinicians from paediatric intensive care, ophthalmology and paediatric tissue viability, paediatric dermatology (if available) or experienced paediatric burns nurses. Additional clinical input to the MDT may be required from infectious diseases, respiratory medicine, haematology, gastroenterology, gynaecology, urology, oral medicine, microbiology, pain team, dietetics, physiotherapy, play specialist, and pharmacy. **Identify one specialist as the team coordinator**.

R21 (GPP) Ensure care is developmentally appropriate and facilities are in place to support both the patient and their relevant carers

R22 (↑↑) Seek* telemedicine advice from a specialist SJS/TEN centre to support local expertise

R23 (↑↑) Admit* without delay to a PICU or Burn Centre with an on-site PICU with experience of treating the following scenarios and with facilities to manage extensive skin loss:

- those with greater than 10% BSA epidermal involvement (including all involved areas of epidermal necrosis, dusky skin and detached skin)
- those with relevant co-morbidities (e.g. underlying malignancy and previous bone marrow transplant)
- those requiring ventilation

R24 (↑↑) Barrier-nurse* in a side room (to reduce nosocomial infections) controlled for humidity, on a pressure-relieving mattress, with the ambient temperature between 25° and 28°C

R25 (↑) Consider transfer* to a specialist centre those with:

- confirmed diagnosis of TEN (>30% skin detachment and SSSS excluded)
- SJS/TEN overlap with other poor prognostic factors
- severe eye disease on presentation who may need access to specialist services, e.g. amniotic membrane transplant
- Where conservative skin care may be supplemented by surgical approach (See R59 and R60)

Currently, specialist centres include burns centre PICU or a PICU with access to a TEN-experienced dermatology service.

Fluid replacement

R26 (↑↑) Monitor* fluid balance carefully and catheterize if clinically indicated

R27 (↑↑) Establish* adequate intravenous fluid replacement; fluid replacement can be guided by urine output and other endpoint measurements (see R29). Fluid replacement should be adjusted daily with careful monitoring of sodium levels.

R28 (↑↑) If vascular access is established*, peripheral venous cannulas should be changed if signs of sepsis or local infection are present, ideally every 2-3 days through non-lesional skin

R29 (↑↑) In severely affected cases, use* continuous invasive haemodynamic monitoring through a central or arterial line to guide fluid resuscitation. Markers of end organ function as a measure of organ hypoperfusion, e.g. urine output plus serial serum lactate, base deficit and serum U&E measurements, may also help to detect tissue hypoperfusion. Be cautious of over-hydration and resultant hyponatraemia. Central-lines should be changed if signs of sepsis or local infection are present, ideally every 5-7 days through non-lesional skin.

R30 (↑↑) Encourage* or increase oral administration of fluids progressively with improvement of mouth involvement

Nutrition

R31 (↑↑) Provide* nutrition early and throughout the acute phase, either by mouth or nasogastric/nasojejunal feeding if adequate oral intake is precluded by buccal mucositis

R32 (↑↑) Involve* a paediatric dietician to advise on nutritional requirements

R33 (↑↑) Perform* a nutritional screen, as stipulated by local policy, within 24 hours of admission including measurement of weight and assessment of re-feeding risk

R34 (↑↑) Measure* weight weekly (minimum) or if the clinical situation changes to support monitoring of nutritional interventions

Analgesia

R35 (↑↑) Use* an appropriate, validated pain tool to assess pain, at least once a day, in those who are conscious

R36 (↑↑) Administer* adequate analgesia to ensure comfort using intravenous opioid infusions in those not tolerating oral medication

R37 (↑↑) Administer* patient-controlled analgesia where appropriate, with involvement of the acute pain team

R38 (↑) Consider sedation or general analgesia where appropriate, to address pain associated with patient handling, re-positioning and dressing changes

R39 (↑) Consider keeping the child sedated and ventilated on ITU for the duration of the acute phase only in extreme circumstances. Beware complications of ventilation such as nosocomial pneumonia and fluid overload

Skin care
(This may involve a conservative (R49-R58) and/or surgical (R59-R62) approach based on a daily review by the specialist MDT of the individual needs of the child or young person with SJS/TEN)

Skin care: applicable to both conservative and surgical approaches

R40 (↑↑) Handle* the skin carefully and reduce shearing forces to minimize the extent of epidermal detachment

R41 (↑↑) Limit* epidermal trauma by avoiding the use of sphygmomanometer cuffs, adhesive ECG leads, adhesive dressings and identification wrist tags

- place thin soft clothing under blood pressure cuff to avoid trauma
- cover the finger-tip with clingfilm before attaching peg oxygen saturation monitor
- use the hands of an assistant as tourniquet and over clothing or soft fabric

- remove the adhesive pad on ECG monitoring leads and secure these with soft silicone tape instead

R42 (↑) Consider soft silicone tapes to attach essential clinical items, e.g. cannula and nasogastric/nasojejunal tube

R43 (↑) Consider silicone medical adhesive remover (SMAR) to remove adherent clothes or wound dressings

R44 (↑) Consider soft bandages or tubular bandage to secure dressings and cannulas

R45 (↑) Consider faecal management system in young people who are immobile and have diarrhoea, to prevent faecal soiling of wounds

R46 (↑↑) Take* swabs for bacterial and candidal culture from areas of lesional skin, particularly sloughy or crusted areas, throughout the acute phase

R47 (↑↑) Take* viral swabs from eroded areas if HSV infection is suspected at any point

R48 (↑↑) Administer* systemic antibiotics only if there are clinical signs of systemic infection. The choice of systemic antibiotic should be guided by local microbiological advice

R49 (↑↑) Encourage* mobilisation

R50 (↑↑) Involve* Physiotherapy for mobilization, those needing respiratory support and in those who are immobile and in need of passive exercises

Skin care: conservative approach

R51 (↑↑) Perform* daily assessment of the extent of skin involvement and epidermal detachment; this should be carried out by a dermatologist or plastic surgeon

R52 (↑) Consider leaving detached lesional epidermis *in situ* to act as a biological dressing; blisters should be decompressed by piercing and expression or aspiration of tissue fluid

R53 (↑) Consider regular cleansing of the wounds and intact skin by irrigating gently using warmed sterile water, saline or an antimicrobial agent, e.g. chlorhexidine (1/5000)

R54 (↑) Consider a greasy emollient, e.g. 50% white soft paraffin with 50% liquid paraffin (50/50 WSP/LP), applied over the whole skin, including denuded areas, every 2 to 4 hours during the acute phase. Aerosolised formulations of emollient can be used for ease of application and to limit epidermal detachment.

R55 (↑) Consider non-adherent dressings applied to denuded dermis and areas of non-involved epidermis to reduce discomfort, and prevent adherence to bed linen and on frictional skin sites (e.g. flexures and genital areas)

R56 (↑) Consider secondary foam or burn dressing to collect exudate

R57 (↑↑) Apply* a topical antimicrobial agent to sloughy areas only (choice should be guided by local microbiological advice); silver-containing products risk systemic toxicity if applied extensively

R58 (↑) Consider applying a very potent topical steroid, e.g. clobetasol propionate 0.05% ointment, to non-detached erythema on skin and mucosal areas, once infection has been excluded or treated

R59 (↑↑) Discuss* transfer to a Burn Centre those with TEN (>30% BSA epidermal loss) and evidence of the following:

- clinical deterioration
- extension of epidermal detachment
- sub-epidermal pus
- local sepsis and/or delayed healing taking into account R58
- where conservative measures may be supplemented with a surgical approach

R60 (↑↑) Discuss* risks and benefits of transfer to alternative specialist unit, depending on severity of condition, comorbidities and relevant local support

Skin care: surgical approach

R61 (↑↑) Perform* regular assessment of the extent of skin involvement and epidermal detachment of exposed wounds; this should be carried out by a burns surgeon

R62 (↑↑) Perform* debridement of necrotic/loose infected epidermis under general anaesthetic. This should only be carried out in a centre experienced in managing paediatric SJS/TEN, i.e. a paediatric burn centre.

R63 (↑↑) Clean* debrided wounds using a topical antimicrobial agent (e.g. chlorhexidine) under general anaesthetic

R64 (↑↑) Apply* physiological closure with biosynthetic dressings to large, confluent areas which have undergone debridement

Mouth care

R65 (↑↑) Instigate* daily oral review during the acute phase

R66 (↑↑) Apply* white soft paraffin ointment to the lips every 2 hours during the acute phase

R67 (↑↑) Clean* the mouth daily with warm saline mouthwashes or an oral sponge

R68 (↑↑) Apply* an anti-inflammatory oral rinse or spray containing benzydamine hydrochloride every 2 to 4 hours, particularly before eating

R69 (↑) Consider offering favourite drinks for oral irrigation rather than standard mouth washes

R70 (↑) Consider a potent topical corticosteroid mouthwash, e.g. betamethasone sodium phosphate, four times a day; in infants, consider clobetasol propionate 0.05% cream or ointment applied topically to affected areas including lips, during acute phase

Eye care

R71 (↑↑) Organise* urgent ophthalmology review. Initial examination should take into account the extent of eyelid, conjunctival and corneal involvement

R72 (↑↑) Instigate* daily ophthalmology review during the acute phase which should include:

- assessment of the integrity of the ocular surface using topical fluorescein eyedrops to stain the extent of epithelial loss on both the cornea and conjunctiva
- removal of pseudomembranes
- breakdown of conjunctival adhesions

R73 (↑↑) Maintain* daily ocular hygiene with local gentle saline irrigation to remove mucous or debris from the ocular surface prior to an inspection of the ocular surface integrity; this should be carried out by an ophthalmologist or specialist ophthalmology nurse

R74 (↑↑) Prevent* corneal exposure in those who are unconscious and at risk of ocular exposure or lagophthalmos. This may be exacerbated by eyelid retraction due to eyelid skin involvement. Use of plastic wrap applied with a thin layer of ointment or petroleum jelly may be indicated where there is significant skin sloughing of the eyelid. Other dressings, as appropriate, may be used to cover the exposed eye, including the use of a long-lasting ophthalmic ointment.

R75 (↑↑) Apply* an ocular lubricant, e.g. preservative-free sodium hyaluronate or carmellose eye drops or preservative-free ophthalmic ointment, every 1 to 2 hours when there is defined ocular involvement during the acute phase

R76 (↑) Consider topical corticosteroid drops, e.g. preservative-free dexamethasone 0.1% twice a day, if there is no suspicion of microbial infection or once it is excluded

R77 (↑↑) 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

R78 (↑) Consider amniotic membrane transplantation (AMT) in presence of conjunctival, epithelial defects or damage

Θ There is insufficient evidence to recommend alternative immunomodulation with topical ciclosporin or topical tacrolimus

Θ There is insufficient evidence to recommend systemic immunosuppression for ocular involvement. Consider on a case-by-case basis following MDT discussion with ophthalmologist, paediatricians and dermatologists.

Urogenital care

R79 (↑↑) Instigate* daily urogenital review during the acute phase

R80 (↑) Consider catheterisation of both boys and girls if required to reduce pain on passing urine and for assessment of fluid balance

R81 (↑↑) Apply* a greasy emollient (white soft paraffin ointment or 50/50 WSP/LP) to the urogenital skin and mucosae every 2 to 4 hours during the acute phase

R82 (↑) Consider a potent topical corticosteroid ointment applied once a day to the involved/affected genitalia surfaces

R83 (GPP) Ensure appropriate management of genital mucosae taking note of issues such as developmental differences in prepubertal girls and relevant child protection issues

R84 (↑) Consider clobetasol propionate 0.05% ointment applied to tampon or vaginal applicator inserted into the vagina. An alternative for younger children may be hydrocortisone foam pessaries.

Immunomodulatory therapy

Θ There is no reliable evidence on the benefits or lack of benefit of any systemic treatments including prednisolone, IVIg, anti-TNF biologics, ciclosporin

R85 (↑↑) If immunomodulatory therapy is instituted, e.g. IVIg, administer* under the supervision of a specialist skin failure MDT in the context of clinical research and/or case registry

Discharge and follow-up

R86 (GPP) Provide written information and direct to available online support e.g. patient support group www.sjsawareness.org.uk

R87 (↑↑) Discuss* potential long-term problems including skin pigmentation changes, skin scarring, nail, eye, oral, dental, respiratory (particularly bronchiolitis obliterans) and urogenital problems

R88 (↑↑) Discuss* the likely cause. If there are multiple potential causes, give balanced advice on the likely risk/benefit regarding re-exposure, e.g. if exposed to analgesia prior to the episode but infection is likely to be cause, it is unnecessary to advise avoidance of all commonly used analgesia.

R89 (↑↑) Discuss* the risk of recurrence if infection is likely to have been the cause

R90 (↑) Consider prophylactic anti-infective treatments e.g. aciclovir for recurrent HSV, or antibiotics in those with recurrent infections causing repeat episodes of SJS/ TEN

R91 (↑↑) If drug allergy is the cause, document* it in their notes, inform all healthcare professionals involved in their care and encourage children/young people to wear a Medic Alert bracelet

R92 (↑↑) Provide* children/young people and their carers/parents with written information about drug(s) to avoid if medication is thought to be the likely cause

R93 (↑↑) Provide* independent counselling when the child is old enough to understand and take responsibility for medication decisions as drug allergy is likely life-long

R94 (↑↑) Report* the episode to the national pharmacovigilance authorities, e.g. the MHRA in the U.K. https://yellowcard.mhra.gov.uk

R95 (↑↑) Liaise* with health visitor or school nurse so they are involved in ongoing support of a school-age child, their siblings and family on discharge

R96 (↑) Consider referral to community children's nurse (CCN) if ongoing help at home is required (wound care, nasogastric/nasojejunal tube or IV treatment)

R97 (↑↑) Organize* an outpatient clinic appointment within a few weeks of discharge

R98 (↑↑) Organize* a paediatric ophthalmology outpatient clinic appointment in cases with ocular involvement. Developmentally appropriate care should be put in place, including long-term, transitional care to adult services.

R99 (↑↑) Offer* appropriate psychological support

R100 (↑↑) Refer* for long-term monitoring with a dermatologist or clinician with relevant expertise

Follow-up investigations

R101 (↑↑) Initiate* appropriate testing to exclude likely culprit infections, e.g. HSV, mycoplasma and chlamydia, which may include serological tests

R102 (GPP) Drug hypersensitivity testing should only be considered in selected cases

R103 (↑↑) 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

List of key future research recommendations (FRRs)

FRR1 National registries or data-collection system for children and young people with SJS/TEN

FRR2 Development of a modified SCORTEN to included children and young people

FRR3 Controlled clinical trials comparing conservative vs. surgical approaches in children and young people with SJS/TEN in standardised settings with detailed analysis of outcome

measures including organ dysfunction and risks of cutaneous complications including pigmentation and scarring

FRR4 Controlled clinical trials comparing an active intervention plus standard supportive care vs. placebo plus standard supportive care (consideration of ciclosporin and anti-TNF use in children and young people)

FRR5 Controlled clinical trials on topical regimens in children, e.g. risks and benefits of topical corticosteroids

FRR6 Impact of nutritional support on paediatric SJS/TEN clinical outcomes

FRR7 Long-term morbidity (including psychological) studies in children and young people with SJS/TEN

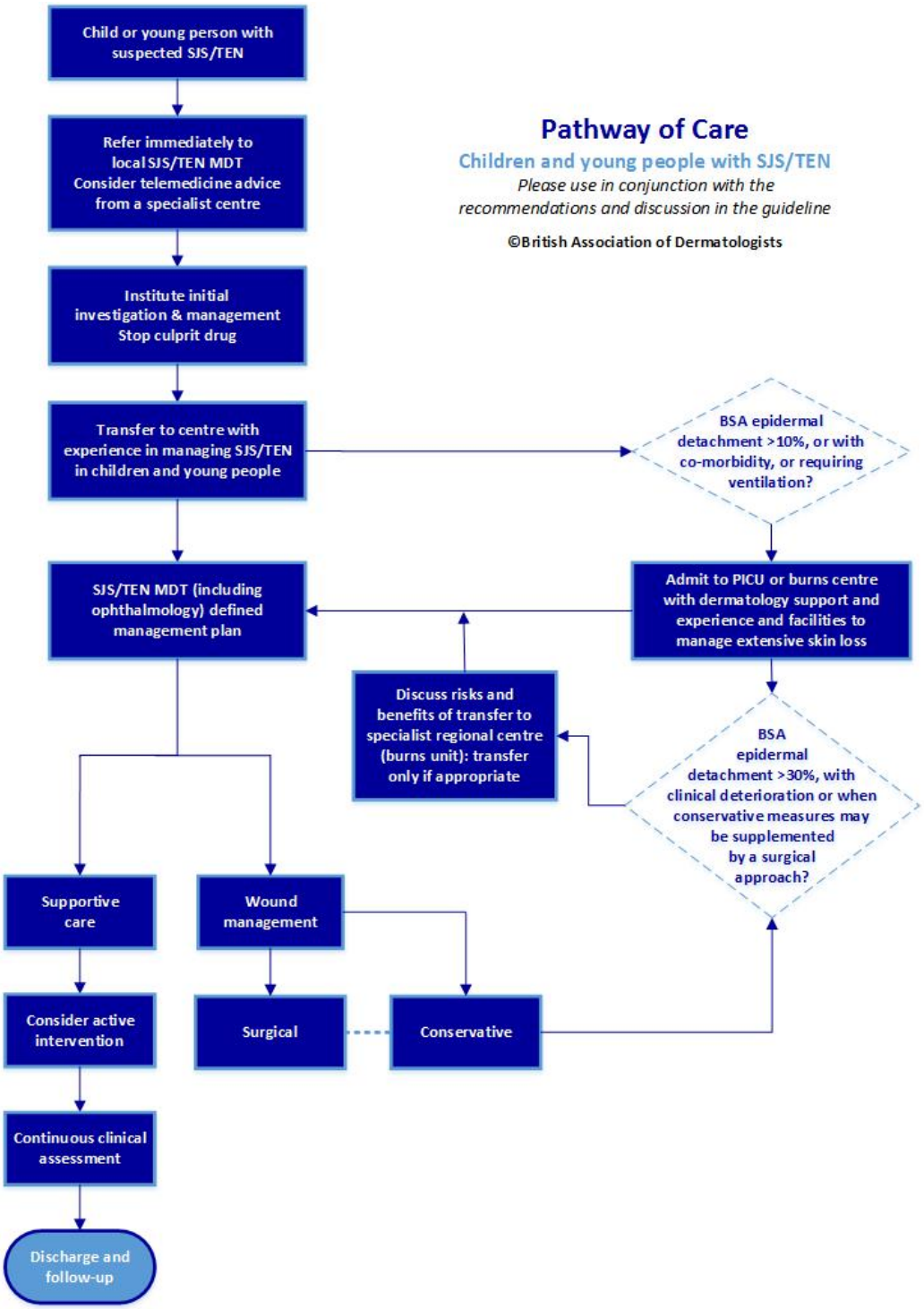
FRR8 Development of a national specialist MDT for the management of SJS/TEN in children and young people

FRR9 Standardization of the reporting of the details on ocular complications in SJS/TEN cases in children and young people

FRR10 National clinical audit on compliance with guideline recommendations

4.0 ALGORITHM

The recommendations, discussions in the LETR (see Appendix B in the supplementary information) and consensus specialist experience were used to inform the algorithm/pathway of care.



5.0 BACKGROUND

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, severe muco-cutaneous reactions, usually to drugs or infections, characterized by blistering and epithelial sloughing.[6] 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, SJS-TEN and TEN in children is approximately 5.3-6.3, 0.7-0.8 and 0.4-0.5 cases per million per year.[7,8] 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 and death. Long-term sequelae in survivors, in particular, ophthalmic, muco-cutaneous and psychological can be severely debilitating.

There are several important differences between SJS/TEN in children/young people and adults including differential diagnosis, aetiological factors, risk of recurrence and outcomes (see Table 2).[9]

	Adults	**Children**
Highest risk	> 80 years	<10 years
Aetiology	Medications > Infections	Infections > Medications
Prognosis	Higher mortality	Lower mortality: preventing long term morbidity is key
Differential diagnosis	Consider immunobullous diseases	Exclude SSSS (mucosal involvement absent)
Recurrence	Unlikely if culprit medication is avoided	More common due to infections as causative agent

Table 2. Differences between adult and paediatric SJS/TEN

Recurrence is more common in children, occurring in up to 18% of cases (10/55)[10] perhaps because the precipitant in children is usually infection (which may recur) rather than drugs (which can be avoided).[11]

The mortality for SJS and TEN appears to be lower in children than adults (see Table 3 and Supplementary information: Appendix G), therefore the management of significant long-term sequelae in the paediatric population is particularly important.

Population		**Mortality**		
	N	**SJS**	**SJS/TEN overlap**	**TEN**
Children (0-17 years, excluding newborns)[7]	1968	0%	3.98%	14.73%
Children (<18 years)[8]	1486	0.35%	3.33%	4.2%
Children & young people (see Appendix G)	661	0%	2.5%	8.55%
Adults (≥18 years) primary diagnosis[12]	3657	3.1%	14.3%	17%
Adults (≥18 years) secondary diagnosis[12]		5.9%	29.5%	15%

Table 3. Mortality in SJS/TEN

6.0 DIAGNOSIS

6.1 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 symptoms. In general, a prodrome of fever, malaise and upper respiratory tract symptoms precedes the eruption by several days but can be difficult to distinguish from a precipitating infection. Ocular inflammation may also develop before skin signs appear. Involvement of the mucous membranes of the eyes, mouth, nose and genitalia is usually an early feature and leads to an erosive and haemorrhagic mucositis. Cutaneous pain is a prominent early feature in SJS/TEN, and the presence of this symptom should alert the physician to incipient epidermal necrolysis. Large areas of confluent erythema develop in severe cases. Lesional skin is tender to touch; minimal shearing forces will cause the epidermis to peel back (Nikolsky sign). Blistering ensues, in which necrotic epidermis separates from the underlying dermis, producing flaccid bullae. Extensive necrolysis results in the detachment of sheets of epidermis, leaving areas of exposed dermis. Denuded dermis exudes serum, becomes secondarily infected (which can cause systemic infections) and readily bleeds.[1]

Despite the striking clinical presentation of SJS/TEN, a number of disorders can present in a similar way with epidermal loss. In children, staphylococcal scalded skin syndrome (SSSS) is cited in the literature as a common 'mimicker' of TEN, but is quite different in its clinical manifestations.[13] In SSSS there is skin loss caused by circulating bacterial toxins to skin-cleavage proteins. However, absence of mucosal involvement distinguishes SSSS clinically from TEN. In cases of diagnostic uncertainty, a skin biopsy or frozen section of a blister roof will identify the plane of cleavage (intraepidermal cleavage = SSSS; subepidermal cleavage = SJS/TEN). Performing a biopsy to exclude immunobullous disorders is rarely necessary in children, but these disorders should be considered, as they may be life threatening, can have a similar plane of cleavage, and require different treatment strategies compared with SJS/TEN (see Table 4). In post-transplant children, the TEN associated with acute graft-vs-host disease (GVHD) can appear identical to drug-induced TEN but differentiation is crucial in this population because they are managed differently.

Erythema multiforme is regarded as a reactive muco-cutaneous disorder that is distinct from SJS/TEN. It is usually precipitated by infection and characterised by typical target lesions that start on acral surfaces and progress proximally. Erythema multiforme major (EMM) is typically accompanied by mucosal erosions and ulceration, usually confined to the mouth. EMM does not progress to SJS/TEN; typically, patients are constitutionally well, make a good recovery, and are rarely affected by long-term complications. Previous publications and reports of SJS/TEN in children and young people may have been biased by misclassification of diseases. This could skew the data on causality and outcomes in paediatric compared with adult populations.

Erythema multiforme major
Staphylococcal scalded skin syndrome (N.B. mucosal involvement should be ABSENT)
Linear IgA bullous dermatosis
Bullous acute graft-versus-host disease
Bullous lupus erythematosus
Bullous Pemphigoid
Epidermolysis bullosa acquisita
Kawasaki disease (early stage erythema no blisters)
Behçet's disease
Generalised bullous fixed drug eruption
Pemphigus vulgaris
Paraneoplastic pemphigus

Table 4. Differential diagnosis of SJS/TEN

6.2 What are clinical phenotypes of SJS/TEN?

SJS/TEN represents a spectrum of reactive disorders with muco-cutaneous involvement.[14,15] NB: Epidermal necrolysis comprises both detached and detachable epidermis. The former is characterised by blisters and epidermal sloughing, the latter by areas of dusky erythema. The following conditions can be differentiated within the spectrum;

- **SJS**: Epidermal detachment less than 10% body surface area (BSA) plus widespread purpule/red macules or flat atypical targets.
- **Overlap SJS-TEN**: Detachment or skin necrosis of 10% to 30% BSA plus widespread purpuric macules or flat atypical targets.
- **TEN**: Detachment or skin necrosis greater than 30% BSA.
- **Respiratory infection induced rash and mucositis**: Significant mucosal involvement with variable cutaneous involvement caused by respiratory infection.

In the paediatric population, both infections and drugs are important triggers of SJS/TEN.[16]

6.3 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 may be necessary to support the clinical assessment and exclude other blistering dermatoses (see Table 4). 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 sub-epidermal vesicle or bulla formation. Adnexal structures 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.[17] SSSS has a more superficial level of skin cleavage and can be differentiated on skin biopsy or frozen skin section if required.

7.0 MANAGEMENT & LONG-TERM COMPLICATIONS

7.1 How should causality be determined?

In the paediatric population, both infections and drugs are important triggers of SJS/TEN. The most commonly implicated medications in children are anti-convulsants and antibiotics (see table 5 and Appendix H).[10,16,18,19] Paracetamol and ibuprofen have an unclear association, and are thought to be likely confounders given their frequent use in treating prodromal symptoms of SJS/TEN. However, there are reports of both causing SJS.[20] One series reported a higher risk of complications in children that had had ibuprofen.[18] New drugs, in particular anti-cancer medications, must also be considered as potential causes.[21]

An algorithm, termed ALDEN (ALgorithm of Drug causality in Epidermal Necrolysis), has been developed to help define drug causality in SJS/TEN.[22] Generally, ALDEN is used as a tool for assessment of drug causality, after the acute phase of illness. However, the key parameters described in ALDEN provide a useful framework for determining drug culpability during acute phase.[1]

Carbamazepine
Trimethoprim/Sulfamethoxazole
Phenobarbital
Phenytoin
Amoxicillin/Amoxycillin
Lamotrigine
Ibuprofen
Paracetamol (Acetaminophen)
Penicillin

Table 5. Commonest drugs causing SJS/TEN in children and young people

Any suspected medication should be withdrawn as soon as possible as this decreases the risk of death.[23] Children with drug-induced SJS/TEN occurring in association with malignancy or stem cell transplantation appear to have a worse prognosis and a higher chance of death. An important differential in this group is acute GVHD and determination of causality and management of immunosuppression can be complex.[24,25]

Referral for diagnostic testing to a specialist centre with an expertise in drug allergy should be considered in severe cases,[26] especially where avoidance of the causal drug is medically compromising or difficult for the patient. Patch testing and/or T cell proliferation/cytokine release assays may be useful in children.[27] Post-exposure diagnostic tests for drug causality are only helpful if the causal drug cannot be established with confidence from the history. In some populations there is a genetic predisposition to SJS/TEN with certain drugs. There is a role for HLA typing in South-east Asians (HLA B 1502) before use of carbamazepine.[28-32]

Infection is a common cause of SJS/TEN in the paediatric population with series reporting up to 50%.[33] Infections that frequently cause SJS/TEN in children include herpes simplex virus, *Mycoplasma pneumoniae,* (up to 50% of reported infections) and others.[34] Relevant testing for infective triggers and discussion with infectious disease team should be considered in all

cases. Certain clinical phenotypes can be specifically associated with infection for example a recently described variant of SJS/TEN secondary to respiratory infection involving predominantly the mucous membrane with limited or absent cutaneous lesions. This has been variably termed 'mycoplasma pneumoniae-associated mucositis' (MPAM),[35] '*Mycoplasma pneumoniae*-induced rash and mucositis' (MIRM),[36] '*Chlamydia Pneumoniae*-induced rash and mucositis' (CIRM)[37] and respiratory infection-induced rash and mucositis (RIRM).[37] It is of relevance to identify this clinical presentation as children may need appropriate anti-infective treatments, are likely to have a good prognosis but there may be a higher chance of recurrence.[36,37]

7.2 What is the best care setting for children and young adults with SJS/TEN?

Children and young people with SJS/TEN should have early assessment by healthcare professionals experienced in the diagnosis and management of paediatric SJS/TEN.

Choice of treatment environment depends on the diagnosis, and the extent and degree of systemic involvement. Children and young people with SJS/TEN should be managed in age appropriate specialist units with an appropriate MDT. Children and young people with limited SJS who are well may be suitably managed on an age-appropriate ward as long as adequate support for skin and mucosal membranes can be provided: in particular, addressing eye disease, nutritional needs and care of skin and genitalia. If there is more extensive skin loss, systemic involvement or co-morbidities, it is vital that children and young people with SJS/TEN are managed in a unit which includes paediatric intensivists and specialists in extensive skin loss (burns surgeons and dermatologists). This will be either a specialised dermatology service PICU or a paediatric burn centre with an on-site PICU. There is limited evidence for any difference in outcomes between specialised dermatology service PICUs and paediatric burn centres. The GDG's experience is that burns services tend to care for children with more extensive skin involvement which would likely skew outcomes.

Children may be less cooperative than adults and may find the hospital setting very overwhelming. Parents and carers are likely to find the experience of their child requiring intensive medical care and being so unwell very frightening. Appropriate strategies to facilitate cooperation with treatments and explanations, update and support are a vital part of the care.

In adults, a delay in transfer to specialised care adversely affects the outcome,[1] and there is some evidence that longer times to referral increase mortality in children and young people.[38-40] Patients do not die of TEN but of complications of TEN; reducing these is paramount. High-risk children (including those with extensive epidermal loss (greater than 70%), high initial SCORTEN, likely medication cause, underlying malignancy or previous stem cell transplantation) need quicker transfer to specialised care.[24,25]

7.3 Specialist Commissioning

Recently, NHS England has confirmed that SJS/TEN will be taken on by highly specialised commissioning from 2019 following specialist review by the Clinical Priorities Advisory Group (www.england.nhs.uk/commissioning/cpag/). This places high priority on patients with SJS/ TEN and aims to reduce variation in standards of care and facilitate research to identify best treatments. Funding has been agreed for a national SJS/TEN service for England and Wales to be provided by a small number of expert centres. Hospitals bidding for this service will have to demonstrate that they can meet the requirements of the detailed service specification, available at www.england.nhs.uk/wp-content/uploads/2018/06/service-specification-stevens-johnson-syndrome-toxic-epidermal-necrolysis.pdf.

Centres will need input from dermatologists, intensivists and specialists in skin loss (plastics and/ or burns). When this service is in place there will need to be clear criteria for which patients are transferred to such centres. In the context of these guidelines we would support all patients with confirmed diagnosis of TEN (>30% skin detachment and SSSS excluded by appropriate biopsy), those with SJS/TEN overlap with other poor prognostic factors and those with severe eye disease on presentation who may need access to specialist techniques e.g. amniotic membrane transplant. Patients with SJS and Mucositis with rash could remain in local centres if appropriate MDT expertise and supportive care are available.

7.4 What are the main aspects of managing children and young adults with SJS/TEN?

Supportive care is the most important aspect in the treatment of patients of all ages with SJS/TEN. This includes care of skin, mucous membranes (ocular, urogenital and oral), resuscitation, fluid balance, nutritional support, analgesia and preventing life-threatening complications and long-term morbidity.[1,41,42] Age-appropriate strategies including play specialists, distraction and involvement of parents should be utilised.

A recent systematic review looking at the effects of systemic treatments concluded that current studies often lack a detailed description of supportive care interventions, and where supportive care was described, variations were observed, especially in the management of detached skin and use of topical treatments.[41] More standardized treatment and reporting are needed in order to compare morbidity and mortality outcomes between different approaches.

7.4.1 *Skin management regimens*

There is limited evidence on the relative risks and benefits of different skin treatments in people with SJS/TEN.[1,41] Expert opinions differ between the merits of conservative and more aggressive approaches. More research is urgently needed as the approach to dealing with detached skin and topical treatments is likely to influence healing, risk of infection and scarring.[41] Scarring is of particular relevance in the paediatric population as a potential long-term sequela with cosmetic and psychosocial impact. Advocates of a more conservative approach believe that, although debridement of epidermis alone will not cause scarring, any procedure which results in dermal trauma risks significant scarring, including hypertrophic

scars. However, supporters of surgical debridement argue that leaving detached epidermis in situ increases the risks of wound infection, deepening wounds and secondary scarring.

Under all circumstances, a conservative approach should be used initially. A more aggressive surgical approach (debridement of detached epidermis following wound closure using biosynthetic dressings) can be considered if conservative management fails, as judged 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 deeper cutaneous defect).

7.5 Do any active immunological treatments impact outcomes?

There is no RCT data on the impact of immunomodulatory therapies. Retrospective data are hard to interpret because of variations in case-mix and timings of treatment regimens, which may be key to their impact and safety. Treatments reported include systemic corticosteroids, IVIg, ciclosporin, thalidomide, cyclophosphamide, TNF-inhibitors, granulocyte colony stimulating factor, plasmapharesis, and haemoperfusion, but there is insufficient data to advocate their use. There is some evidence that ciclosporin benefits adults, with a meta-analysis reporting no deaths and a regression model revealing a significant beneficial effect compared with supportive care alone.[41] A recent RCT shows some promise for the role of anti TNFs and this is likely to be an active area of research.[43]

In children and young people, systemic corticosteroids and IVIg are the two most commonly used treatments, but data remains limited. For now, the decision to administer systemic medications should be taken by an expert based on individual circumstances. The relative frequency of infection as the precipitant in children, compared with adults, must be taken into account in future studies of immune-suppressive therapy.

7.5.1 Systemic corticosteroids

Individual case reports indicate that early administration of systemic glucocorticosteroids may limit disease progression and reduce morbidity and mortality. However, there are no large studies documenting this. Studies reporting good outcomes tend to be retrospective and uncontrolled.[44-46] A meta-analysis that included 96 studies and 3248 patients of all ages suggests a survival benefit with glucocorticosteroids, but this was significant in only one of three statistical analyses.[41]

There is also conflicting data on the efficacy of systemic treatment in limiting ocular disease. Power *et al.* showed no benefit of systemic corticosteroid in acute SJS or TEN but there were no separate data for the paediatric age group.[47] The study by Kim *et al.*, showed a significant improvement, between initial and final visits, in best-corrected visual acuity and mean ocular involvement score (OIS) in adults but not in children treated with corticosteroid or IVIg, either separately or combined with amniotic membrane.[48]

The concern is that systemic corticosteroids may increase the risk of infection, and should therefore be used with caution. A retrospective case series reported two deaths on those treated with prednisolone.[49]

7.5.2 IVIg

In adults, consensus is that IVIg does not have a major impact on outcomes;[1,50,51] however, there is some data showing a beneficial effect in children. Studies are difficult to interpret without clear information about disease characteristics and severity, and the dosing and timing of IVIg. RCTs will be needed to ascertain whether the apparent benefit of IVIg in paediatric cases simply reflects the more favourable prognosis in this age-group.

Good outcomes have been reported in several case series of paediatric SJS/TEN. [52,53] A systematic review presented data on 33 children with TEN and six with SJS-TEN overlap, all of whom received IVIg treatment (0·25–1·5 g kg^{-1} daily; 1–5 days), with no deaths reported.[54] Shorter lengths of hospital stay, fewer deaths, and faster healing times have also been reported in retrospective studies in children and young people treated with IVIg.[50,52,55] The role of IVIg in ophthalmic disease in children and young people remains unclear. Small case series and anecdotal uncontrolled and unpublished series suggest that systemic immunosuppression (including IVIg) may reduce long term keratopathy and subconjunctival fibrosis although further research is required.[48,56-58] However, IVIg can have adverse effects, particularly renal impairment,[1,59] and in one paediatric series, higher rates of ophthalmic complications were seen in children given IVIg compared with those who were not.[10]

7.6 What are chronic complications of SJS/TEN and can these be prevented?

SJS/TEN has a low mortality in children and young people so prevention of long-term complications is extremely important. These include ophthalmic, genito-urinary, dental,[60] cutaneous (including long term pigmentary changes and nail changes), gastrointestinal, respiratory and psychological. The respiratory complication bronchiolitis obliterans can be severe in children. This can occur at any stage of the illness, including after discharge and respiratory function should be expertly monitored.[61,62] Psychological complications are now well recognised in adults and include post-traumatic stress disorder and fear of taking medication.[63-65] In children further work on psychosocial implications is needed to assess impact both short and longer term and potential impact of long-term cosmetic consequences. Both patients and their families should be offered appropriate support.[29]

Eye disease is a frequent complication and has arguably the greatest long-term morbidity and requires particular and urgent attention both in short and long-term.[1,66]

7.6.1 Ocular Complications of SJS/TENS in Children.

Ophthalmological expertise is required as soon as SJS/TEN is diagnosed to minimise ocular complications. This guideline deals primarily with acute and subacute stages of SJS/TEN but the most serious and sight-threatening complications occur later. As discussed, mortality in

children is lower than in adults, so a greater proportion with severe ocular complications will survive.

Incidences of ocular involvement vary from as low as 39.3%[67] to 71 – 100% in other series,[68,69] but the lower incidences of ocular involvement in children in some reports may have been due to inclusion of cases of erythema multiforme.[67] The incidence of ocular involvement may be slightly greater in TEN compared with SJS.

Involvement of the eye in SJS/TENS can be divided into acute, sub-acute and chronic stages (Table 6).[70] The timing of these complications overlaps considerably and may be accelerated in more severe cases.

Early ocular diagnosis and treatment are essential, because eye disease evolves rapidly causing damage with long-term sequelae. Ocular inflammation can persist long after the skin has healed, therefore there should be long-term ophthalmology follow-up.[71] The management of long-term ocular sequelae is outside the scope of this article.

	ACUTE (within first 7 days)	SUBACUTE (within the first 6-8 weeks or until discharge from burns ICU)	CHRONIC (beyond 6-8 weeks or occurring after discharge from burns-ICU)
EYELIDS	Eyelid oedema; Eyelid margin desquamation and sloughing; eyelash loss	Ankyloblepharon Anterior blepharitis Trichiasis	Ankyloblepharon Entropion Trichiasis Eyelid margin keratinisation Destruction of Meibomian glands / distichiasis Punctal auto-occlusion / stenosis
CONJUNCTIVA	Bulbar and palpebral conjunctival hyperaemia; Subconjunctival haemorrhages; Bubar and palpebral conjunctival pseudomembranes Ulceration of conjunctiva, epithelial erosion and positive staining with fluorescein	Symblepharon Conjunctival adhesions Episcleral injection / scleritis	Progressive or non-progressive bulbar and tarsal subconjunctival scarring; Symblepharon; Loss of conjunctival goblet cells;[72] Scarring and loss of lacrimal gland ducts and accessory lacrimal glands; Keratinisation of conjunctiva;[73] Dry eye; Recurrent inflammation[74] / scleritis Mucous membrane pemphigoid reaction[71]
CORNEA	Punctate epithelial erosions Corneal epithelial loss and ulceration	Corneal haze	Loss of corneal limbal stem cells; Conjunctivalisation of cornea; Corneal vascularisation; Persistence of recurrent corneal epithelial defects; Opacification of cornea

Table 6. Involvement of the eye in SJS/TENS

8.0 RECOMMENDED AUDIT POINTS

A recommendation to commissioners that all specialist centres should perform regular audits. Data collection should be coordinated between centres including details of management (including timing and dosing regimens for any medications) used for each case of SJS/TEN and patient outcomes.

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

1. Has causality assessment been undertaken within the first 24 hours of admission including drugs and/ or infection?
2. Has diagnostic biopsy or frozen skin section been taken if any diagnostic uncertainty?
3. Has child been cared for in an appropriate environment (reflecting both disease extent and the age of the child)?
4. Has the patient been seen by an ophthalmologist within 24 hours of diagnosis? Have daily ocular assessments been made throughout the acute phase?
5. 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?
6. Has an appropriate MDT been involved in care including all relevant specialties?
7. Has outcome including mortality and any identified long-term morbidities been documented?
8. At discharge, has:
    a. contact been made with the patient's GP?
    b. the patient and/or the parents/carers of the patient been counselled about:
        i. future avoidance of culprit drug(s) if likely?
        ii. the risk of recurrence in particular if likely infectious aetiology
        iii. the long-term sequelae, including psychological

STAKEHOLDER INVOLVEMENT AND PEER REVIEW

The draft document and supporting information was made available 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), Royal College of Paediatrics and Child Health (RCPCH), British Society for Paediatric and Adolescent Gynaecology (BritSPAG), British Society for the Study of Vulval Disease (BSSVD), Association of Paediatric Anaesthetists of Great Britain and Ireland (APAGBI), Association of Anaesthetists of Great Britain and Ireland (AAGBI), Paediatric 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.

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.

PLANS FOR GUIDELINE REVISION

It is envisaged that the proposed revision, scheduled for 2021, will combine both this guideline and the published adult version;[1] where necessary, important interim changes will be updated on the BAD website.

SUPPORTING INFORMATION

Additional supporting information including the study selection PRISMA flow diagram, summary of narrative findings, LETR, list of excluded studies, search strategy and a template discharge letter may be found in the online version of this article.

ACKNOWLEDGEMENTS

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Footnote:

This is a new guideline 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: NJ Levell [Chairman T&G], PM McHenry [Chairman T&G], TA Leslie, S Wakelin, RYP Hunasehally, M Cork, GA Johnston, N Chiang, FS Worsnop, P Rakvit, A Salim, B McDonald, SL Chua, D Buckley, G Petrof, F Hussain, A Bardhan, N Callachand [British National Formulary], T Flavell [British Dermatological Nursing Group], AA Salad [BAD Scientific Administrator], LS Exton [BAD Guideline Research Fellow], MF Mohd Mustapa [BAD Clinical Standards Manager].

DECLARATIONS OF INTEREST

TMcP: invited speaker - Leo Pharma, AbbVie (non-specific); sponsorship to conferences – AbbVie, Novartis (non-specific); organiser of the BSPD in Oxford 2015 (non-specific); SB: invited speaker - Novartis (non-specific); RM, DC, PD, LN, AEY, GNW, KLT, LSE, MFMM, patient carer representatives and patient representative: None

SUPPLEMENTARY INFORMATION 1

Appendix A: Review Protocol
Appendix B: Linking Evidence To Recommendations (LETR)
Appendix C: Narrative findings for non-comparative studies
Appendix D: Narrative findings for non-comparative studies (no treatment details)
Appendix E: Narrative findings for non-comparative studies (ocular complications)
Appendix F: Commonest drugs causing SJS/TEN in non-comparative studies
Appendix G: Mortality summary from non-comparative studies
Appendix H: PRISMA diagram – study selection
Appendix I: Papers excluded from quantitative analysis
Appendix J: Methodology
Appendix K: Search strategy

SUPPLEMENTARY INFORMATION 2:

Discharge letter

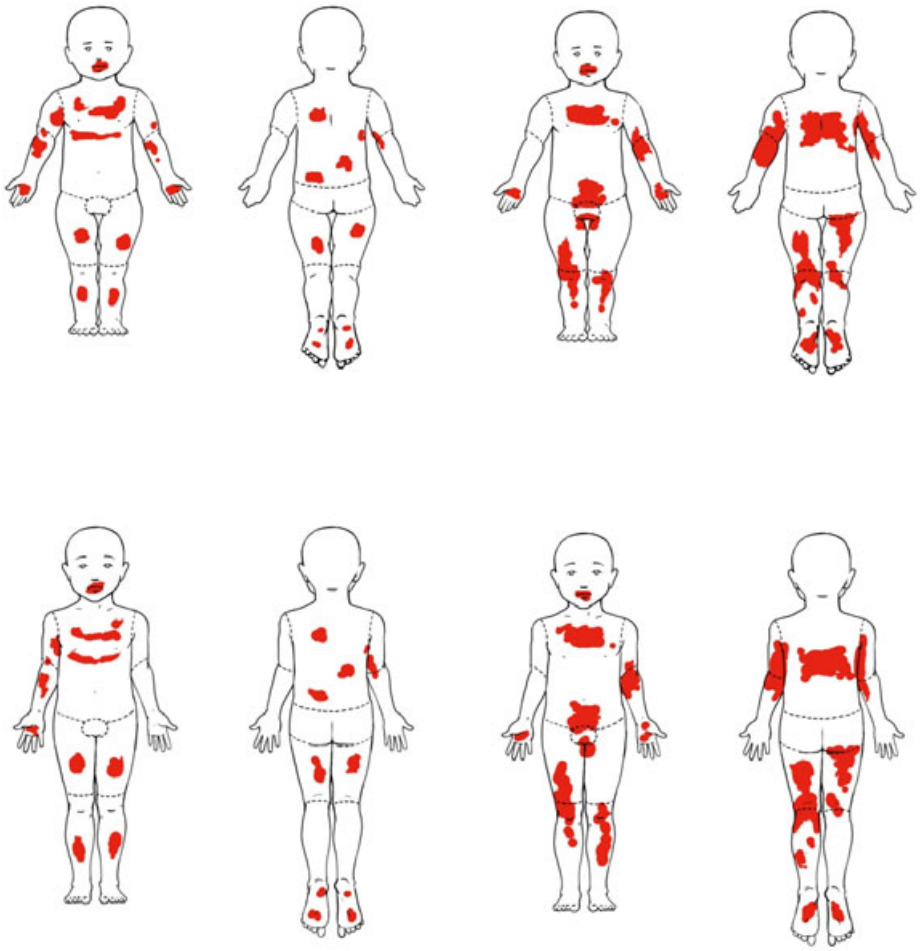

Fig 1. Body map schematics demonstrating examples of skin involvement in SJS/TEN. Top (≤2 years) & bottom (>2 years): Left (front and back): extent of epidermal detachment (in red) 10% BSA. Right (front and back): extent of epidermal detachment (in red) 30% BSA. Adapted from Figure 13 in the UK guidelines for the managements of SJS/TEN in adults 2016[1]

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