‘Medical skin loss’: Stevens–Johnson syndrome/toxic epidermal necrolysis and staphylococcal scalded skin syndrome

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Key points

- Severe exfoliative skin conditions leading to major skin loss are rare, yet associated with significant morbidity and mortality, and often necessitate critical care input.
- These conditions are complex and need a multidisciplinary approach to management with input from intensivists, plastic surgeons, dermatologists, ophthalmologists, dieticians, psychologists, and physiotherapists.
- Skin failure from widespread skin loss constitutes another organ failure. It should be treated like a major burn.
- Strict attention to fluid and electrolyte balance, temperature management, eye care, wound care, pain control, nutrition, and prevention of infection are key.
- Early referral with subsequent transfer to a burns centre for specialist wound management is highly recommended and improves outcomes.

Several acute exfoliative skin conditions lead to major skin loss and require critical care treatment. Although rare, these conditions have high mortality rates, long critical care stays, and are associated with significant chronic morbidity. Included in this group are Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and staphylococcal scalded skin syndrome (SSSS). Widespread skin loss from these conditions leads to ‘acute skin failure’ which is comparable with any other major organ dysfunction. It is characterized by pain, loss of water, electrolytes and protein, altered thermoregulation and immune function, hypermetabolism, and increased cardiac output.1 Understanding the structure and function of skin improves our ability to care for these patients. Many of the challenges associated with managing these conditions are similar to those seen in patients with a major burn. Hence, these cases are most appropriately managed in specialized burns centres with access to multidisciplinary expertise including intensivists, plastic surgeons, dermatologists, ophthalmologists, dieticians, psychologists, and physiotherapists. Early input from other disciplines optimizes long-term outcomes.2

Current burns data suggest 60–80 cases of SJS/TEN and SSSS are admitted to burns critical care units in the UK per annum over the past 5 yr. In addition, intensive care national audit and research centre data recorded 132 cases admitted to general adult critical care units between 1995 and 2006.3 Compared with average general adult critical care patients, these patients had a higher mortality rate and longer critical care stay. The relative rarity of these conditions makes it difficult for individual clinicians to gain experience in managing these cases. This article, therefore, aims to cover the main critical care and anaesthetic considerations with regard to major skin loss during critical care admission.

Other infective skin conditions such as necrotizing fasciitis and dermatological malignancies are beyond the scope of this article.
Skin structure and function

The skin is the largest organ of the body, accounting for 15% of total body weight and has a surface area of 1.7 m² in the average adult. Human skin consists of three layers; the epidermis, dermis, and the supporting hypodermis or ‘subcutis’ (Fig. 1).

Epidermis

This is a stratified squamous epithelium derived from embryonic ectoderm. The keratinocyte is produced in the basal layer of the epidermis. These immature cells proliferate and differentiate as they migrate towards the surface forming several well-defined layers that are constantly replenished. The outermost layer, the stratum corneum, consists of flattened keratinized cells (corneocytes) that are shed every 2–3 weeks. Transmission of biochemical messages to lower layers in response to injury regulates their activity.

Dermis

This is a layer of connective tissue composed mainly of collagen (70%), elastin, and a semi-solid matrix of glycosaminoglycan. This connective tissue matrix provides strength, structure, and elasticity to the dermis and is formed by fibroblasts. Nerves and free nerve endings responsible for transmission of pain, itch, and temperature are found in the dermis in addition to specialized sensory receptors. There is also a rich vascular plexus located within the dermis.

Regeneration of the epidermis requires the presence of the dermis. If the dermis is totally destroyed such as with a full thickness burn, skin is unable to heal.

Specialized cells of the skin

Skin contains a variety of specialized structures referred to as epidermal appendages. These include hair follicles, arrector pili muscles, sebaceous glands, eccrine and apocrine sweat glands, melanocytes, Merkel cells, and Langerhans cells.

Functions of skin

The skin is a complex organ with many functions, which are crucial to survival. These are given in Table 1.

Stevens-Johnson syndrome and toxic epidermal necrolysis

SJ S and TEN are severe muco-cutaneous reactions characterized by erythema, extensive epidermal necrosis, and widespread bullous epidermal detachment. They are most commonly triggered by drugs and affect all age groups.

SJ S and TEN are variants of the same disease spectrum, but distinguished chiefly by severity. SJ S is the less severe form, affecting <10% total body surface area (TBSA). TEN is more severe and affects >30% TBSA. Cases which affect 10–30% are referred to as SJS/TEN overlap.

In total, 90% of cases involve mucous membranes of the mouth, eyes, and genital tract. This rare condition has an annual estimated incidence of 0.4–1.2 cases million⁻¹.

Causes

The common drugs that trigger TEN are listed in Table 2. The onset of symptoms is typically 4–28 days after introduction of the drug, but can be delayed. Infection with Cytomegalovirus and Mycoplasma are the next most common triggers of TEN.

Other predisposing factors include:

(i) Human immunodeficiency virus infection
(ii) Malignancy or bone marrow transplantation
(iii) Genetic susceptibility (e.g. human leukocyte antigen B×1520).

Pathophysiology

The mechanism of TEN is not fully understood. However, it is characterized histologically by keratinocyte apoptosis and
separation of the epidermis from the dermis at the dermo-epidermal junction. This leads to extensive epidermal destruction. This process is thought to be mediated by cytokines including fas-fas ligand and tumour necrosis factor alpha either by triggering an immune reaction involving CD8+ lymphocytes or from a direct toxic effect of the drug or its metabolite.

Clinical features

The onset of TEN is typically preceded by a prodrome for 2–3 days of fever, flu-like illness and malaise before the development of skin blistering, erosions, and tenderness of the skin. Mucous membranes of the eyes, nose, mouth, and genitalia are commonly affected early in the course of the disease and result in an erosive and haemorrhagic mucositis. Involvement of the respiratory and gastrointestinal (GI) tract epithelium can also occur.

The early cutaneous lesions tend to be atypical target-like lesions. The erythematous macules with purpuric centres then become diffuse and confluent reaching a maximum over the next 5–7 days. Bullae and skin sloughing result in large areas of denuded epidermis. Nikolsky’s sign is present, where gentle lateral pressure results in sheet-like epidermal detachment (Fig. 2A). Separation of this necrotic epidermis leaves areas of exposed, raw, dark red dermis that readily bleeds (Fig. 2B).

History of introduction of a drug associated with a high risk of SJS/TEN within 4–28 days is classical.

Estimation of skin involvement can be done using the Wallace rule of nines or the Lund and Browder chart as a rough guide, though often affected areas are non-confluent and patchy (Fig. 3).

Diagnosis is suggested by the clinical picture, but skin biopsy demonstrating variable epidermal loss and vesicle or bulla formation in the basal layer is useful to support the diagnosis and exclude other blistering skin disorders.

Specific management: TEN

Early recognition and withdrawal of any potentially causative agent is crucial. These drugs require reporting to the medicines and healthcare products regulatory agency. Careful consideration needs to be given to minimizing medication and limiting introduction of new medicines to prevent complications (e.g. deep vein thrombosis prophylaxis, GI protection).

Although there is no definitive treatment for TEN, several adjuvant immunomodulating therapies have been trialled. These include the use of immunoglobulins, corticosteroids, and ciclosporin. However, as a result of the rare nature of SJS/TEN, studies are limited and evidence-based standards are difficult to define. This is reflected in variable treatment practices across burns centres over the past two decades. In Maher and colleagues’ review of 20 studies, 8 studies reported using i.v. immunoglobulin in the course of treatment and 6 studies reported the use of systemic corticosteroids.

**Table 1 Functions of skin**

<table>
<thead>
<tr>
<th>Function</th>
<th>Description</th>
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<tbody>
<tr>
<td>Protection</td>
<td>Barrier function of stratum corneum protects against environmental, chemical, and microbial hazards. Limitation of inward and outward passage of water and electrolytes ensures the conservation of the internal milieu. Durability and elasticity of dermis contributes to protection against physical injury. Melanin production protects against ultra-violet radiation.</td>
</tr>
<tr>
<td>Regulation</td>
<td>Temperature homeostasis is maintained by alteration of skin blood flow, sweating, and pilo-erection. Minor role in maintaining fluid balance by avoiding excessive evaporative water loss that would otherwise cause dehydration and cooling.</td>
</tr>
<tr>
<td>Immune</td>
<td>Dynamic role in innate and acquired defence systems.</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Role in Vitamin D synthesis Capability in transformation of some drugs</td>
</tr>
<tr>
<td>Neurosensory</td>
<td>Terminal fibres of sensory nerves and specialized sensory receptors lying within the dermis enable skin to act as a large sensory organ.</td>
</tr>
<tr>
<td>Social interaction</td>
<td>Visible portion of body covering</td>
</tr>
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**Table 2 Medication associated with high risk of TEN**

- Allopurinol
- Carbamazepine
- Lamotrigine
- Phenobarbital
- Phenytoin
- Cotrimoxazole
- Sulfadizine
- Oxicam NSAIDs
- Nevirapin

*Fig 2 (a) Nikolsky sign. (b) Large area of denuded skin in TEN*
Thalidomide use in TEN has been studied in a randomized control trial but found to be harmful. The use of plasmapheresis and TNF inhibitors has been reported in a few case series.

**Immunoglobulin**

The use of i.v. immunoglobulin (IVIG) was first studied by Viard and colleagues in 1998. Its proposed mechanism of action is based on its antagonizing effect on fas ligand activity, which has a role in mediating keratinocyte apoptosis in TEN. Since 1999, the use of IVIG for TEN remains controversial because of the limited evidence base. However, use has become more frequent in the past decade and the Department of Health lists TEN as a condition for which IVIG use is appropriate in the short term. Adverse effects include renal impairment, haemolysis, and thrombotic complications.

The St Andrew’s Centre currently use IVIG in suspected cases of TEN at a dose of $1 \text{ g kg}^{-1}$ (ideal body weight) for 3 days. Current data suggest that IVIG treatment is more effective if used early.

**Systemic corticosteroids**

Sub-analysis of patients from the EuroSCAR and RegiSCAR trials have not shown any benefit from steroid therapy in TEN,
though some studies have initially shown values in reducing inflammation and, in particular, reducing ocular complications. There is a theoretical risk of increased sepsis and impaired re-epithelialization leading to increased mortality. I.V. corticosteroids are currently not recommended.

Ciclosporin

The immunosuppressant effects of ciclosporin are directed towards T-cell function, which play a role in the propagation of keratinocyte apoptosis in TEN. Studies use a dose of 3–5 mg kg$^{-1}$ for 8–24 days. Adverse effects include hypertension, worsening renal function, and infection. There has been no firm conclusion regarding benefits because of the small number of published studies.

Prognosis

The overall mortality rate for SJS is 10%, but increases to 30–50% in TEN. The main cause of in-hospital mortality is multi-organ failure from sepsis. Age and extent of skin involvement are major prognostic factors. The SCORTEN (severity of illness score for TEN) is a validated scoring system, which predicts mortality from TEN based on seven clinical parameters. $^9$ This should be scored within 24 h of admission. Each parameter scores 1 point (Fig. 4).

Staphylococcal scalded skin syndrome

This is a staphylococcal toxin-mediated exfoliative dermatitis that can result in major skin loss because of widespread splitting of the granular layer of the epidermis. It primarily affects children <6 yr with low renal maturity and hence reduced metabolism and decreased excretion of staphylococcal toxin. Adults who are affected commonly have underlying disease that increases their susceptibility to staphylococcal infection.

Pathophysiology

SSSS is caused by two distinct epidermolytic exotoxins, ETA and ETB. These exotoxins cause cleavage of the desmoglein 1 complex, a desmosomal adhesion molecule responsible for the anchoring of keratinocytes. This results in the formation of fragile tense bullae. These toxins are also implicated in bullous impetigo. Widespread splitting of the epidermis results in superficial diffuse sheet-like desquamatization.

Although the diagnosis is clinical, skin biopsy will classically show cleavage of the stratum granulosum.

Clinical features

SSSS presents with a prodromal illness of fever, malaise, irritability, sore throat, or conjunctivitis. Blistering of the skin develops over the next 48 h. Lesions often affect the flexures initially before generalized scaling and sheet-like desquamatization over the next few days (Fig. 5). Nikolsky’s sign can be present revealing a moist erythematous dermal base. Mucosal lesions are rare.

Estimation of skin loss can be done in children using the Lund and Browder chart (Fig. 3).

Specific management: SSSS

Antibiotic therapy directed at staphylococci along with supportive therapy and good wound care is the mainstay of treatment. Cultures should be taken from blood, urine, nasopharynx, skin lesions, and any site of potential infection.

Prognosis

In the absence of systemic complications, complete healing without scarring or altered pigmentation can occur in 10–14 days. Mortality from SSSS is 4% in children. The main cause of morbidity and mortality are sepsis and electrolyte imbalance. In adults, the mortality rate is up to 60% because of underlying disease.

General management of major skin loss

Meticulous supportive care forms the mainstay of treatment for major skin loss. Management in a critical care unit or specialized burns unit for optimal wound care is appropriate for skin involvement of >10%. Wound infection is a major threat to wound healing by deepening of the skin loss, but can also be life-threatening because of resultant bacteraemia and multi-organ failure. Where possible, lines should be inserted through unaffected skin.

Fluid management

Fluid resuscitation is often required in the early stages as many patients present with fluid deficit from poor oral intake and increased transcutaneous fluid loss. Initial requirements are less (by a third/quarter) than that required for a burn of similar size as predicted by the Parklands formula; $4 \text{ mg kg}^{-1} \% \text{ burn}^{-1}$.

Maintenance fluid needs to account for variable, but often significant ongoing insensible losses from skin and should be guided by clinical parameters aiming for urine output of $0.5 \text{ ml kg}^{-1} \text{ h}^{-1}$.

![Fig 4 SCORTEN.](https://academic.oup.com/bjaed/article-abstract/16/3/79/2897752/14)

![Fig 5 Staphylococcal scalded skin syndrome.](https://academic.oup.com/bjaed/article-abstract/16/3/79/2897752/15)
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(1 ml kg⁻¹ h⁻¹ in children). The use of vasopressors may be required, but should be avoided if possible as they may reduce blood flow to the skin and limit wound healing.

Children with skin involvement >15% require catheterization.

Temperature management

Significant heat loss from radiation and evaporation occurs from skin loss. Patients should be nursed in a side room where ambient temperature can be raised to 25–28°C and humidity can be adjusted. The use of warming devices, such as warming blankets, is recommended. Both core and peripheral temperature should be monitored to maintain a core–peripheral temperature gradient of <2°C.

Wound care

There are several approaches to skin care. Surgical debridement to remove the detached skin and necrotic tissue is the main approach in many burns units and reflects the current approach to care of burns patients. This requires a general anaesthetic. Other centres advocate more conservative management and restrict aggressive debridement. Currently, there is no evidence to suggest that either approach is superior. Subsequent coverage of the wounds is essential to reduce infection and to promote effective wound healing. The St Andrew’s Centre wound management algorithm is shown in Figure 6. It includes the use of versajet hydrosurgery in patients who present late (>2 days) or whose wounds appear infected.¹⁰

Ideal dressings should maintain a moist environment, be permeable to gas exchange and impermeable to bacteria. They should provide a degree of thermal insulation and be able to be removed without trauma. Non-adherent nanocrystalline silver dressings (e.g. Acticoat™) have good antimicrobial efficacy and has been successfully used as the primary dressing. Dressings impregnated with silver sulfadiazine should be avoided in cases of TEN triggered by a sulfonamide. Biosynthetic skin substitutes such as Biobrane® have also been used as a primary dressing. It is effective in reducing pain and exudative losses and limits microbial colonization. It remains intact for up to 7 days before becoming detached and hence can decrease the frequency of painful dressing changes. This also minimizes disruption to the healing skin. Application requires a general anaesthetic.

Gentle skin handling and limitation of trauma to the skin from blood pressure cuffs, adhesive electrocardiogram electrodes, and line dressings is required. Day-to-day care is best undertaken by specialist nurses who are familiar with managing fragile skin.

Infection

Wound infection with Pseudomonas, Staphylococcus, and Enterobacter is common and can limit recovery by impairing re-epithelialization and contributing to sepsis and multi-organ failure. Sterile handing where possible and regular use of antimicrobial solutions for disinfection such as Octenisan® are recommended. Frequent wound swabs for culture are required for microbiological surveillance and to guide antimicrobial therapy. There is no indication for the prophylactic use of systemic antibiotics in patients with SJS/TEN as this may increase skin colonization with Candida.

The use of bowel management systems is useful to prevent soiling of wounds from faeces.

Fig 6 St Andrew’s Centre wound management algorithm.
Patients often require critical care therapy for prolonged periods and are at risk of usual critical care infections. General critical care precautions in infection control including strict barrier nursing is required to prevent cross contamination and nosocomial infections.

**Mouth and airway involvement**

Mucosal involvement of the lips, tongue, and palate is frequent (Fig. 7). When severe, haemorrhagic erosions can extend to affect the oropharynx, oesophagus, larynx, and respiratory tree. Fibre-optic bronchoscopy may demonstrate bronchial epithelial detachment in the proximal airways. Subsequent development of pulmonary infiltrates, bronchial obstruction, and hypoxaemia may prompt the need for mechanical ventilation. Washout of necrotic bronchial epithelium during fibre-optic bronchoscopy is useful.

Intubation and mechanical ventilation may be required in the absence of respiratory involvement to facilitate the general management of patients with severe skin loss. In the acute stages, it may be required to enable safe transfer, aids with effective pain relief and airway protection from excessive epithelial necrosis, and haemorrhagic erosions of the upper airway.

**Pain management**

Major skin loss is painful and a holistic approach is required. Inadequate pain control leads to psychological trauma and has a marked adverse effect on long-term psychological outcome.

Patients generally require opioids to maintain adequate background analgesia. Additional analgesics are necessary for the increased pain associated with positioning and wound handling. Sedation may also be required for procedures such as dressing changes. Options for this include the use of ketamine, propofol, midazolam, and remifentanil.

Regular use of analgesic adjuncts such as ketamine, clonidine, and gabapentin are useful in combination with opioids because of their opioid-sparing effects. However, careful consideration is required before using gabapentin in patients with SJS/TEN triggered by anticonvulsants. These adjuncts can be reduced and adapted during the course of healing.

**Nutrition**

Poor oral intake in combination with increased calorie requirements can result in weight loss. Calories in addition to those required to sustain basal metabolic rate are required for the increased energy expenditure from the stress factor because of skin loss and hypermetabolism. This is not to the same extent as that seen with burns. Input from a dietician for assessment of calorie requirements is important and requires adjustment from the early catabolic phase to the anabolic recovery phase.

Continuous nasogastric or ideally nasojejunal feed should be established as soon as practical to support metabolic disturbances. Regular weighing is recommended to monitor nutritional state.

**Eye care**

Immediate and regular ophthalmology review is necessary to assess for ocular involvement and secondary ophthalmic complications in SJS/TEN. Early effective management can reduce the severity of chronic eye disease including permanent visual impairment and blindness. Patients require frequent eye lubricants and topical preservative free antibiotics in the presence of corneal ulceration or proved ocular infection. Ocular hygiene including glass rodding to prevent against adhesions is required on a daily basis.

**Prevention of urogenital and vulvovaginal sequelae**

Examination of the urogenital tract should form part of the initial and subsequent daily assessment of SJS/TEN as blistering and erosions occur. Long-term urinary and sexual dysfunction can result from urethral strictures and vaginal adhesions. In women, formal gynaecological review is recommended for consideration of the use of vaginal dilators or vaginal moulds to prevent against vaginal synaehiae. Application of corticosteroid creams, antimicrobial creams, and white soft paraffin ointment to involved areas is appropriate and coverage with a non-adherent dressing such as gelonet or Mepitel™. Uncircumcized males need to be checked for preputial retractability.

**Summary**

Major skin loss from exfoliative dermatoses is rare but life threatening and often necessitates critical care input. It is associated with marked physiological abnormalities, which lead to higher mortality and longer critical care stays than average for adult patients. The resulting ‘skin failure’ should be regarded as a distinct entity analogous to any other organ failure.

The rarity of SJS/TEN and SSSS leads to difficulty in gathering high-quality evidence on specific immunomodulating treatment options. Hence, there is a lack of consensus among clinicians and varied treatment practice. Above all, withdrawal of the culprit drug in cases of SJS/TEN and early appropriate antibiotic therapy in cases of SSSS is required in combination with meticulous supportive care. This is best carried out in a specialized burns unit with expert multidisciplinary input.

**Declarations of interest**

None declared.

**MCQs**

The associated MCQs (to support CME/CPD activity) can be accessed at [https://access.oxfordjournals.org](https://access.oxfordjournals.org) by subscribers to BJ/A Education.
References


