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WOUND CARE (H LEV-TOV, SECTION EDITOR)

Wound Management in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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Abstract

Purpose of Review Stevens-Johnson syndrome and toxic epidermal necrolysis are severe mucocutaneous drug reactions associated with a potentially high mortality rate. They are characterized by epidermal necrosis and extensive detachment. For these reasons, wound care is a fundamental component of patient management. However, there is a lack of evidence-based data, and treatment approaches can vary drastically between institutions. Our aim was to analyze the available studies on this topic as an attempt to review various management strategies.

Recent Findings Considering the rarity, variable presentations, and difficulty to prospectively study patients with SJS/TEN, there is a lack of evidence-based data on the topic of wound management. We reviewed the most recently published guidelines, expert opinions, and other studies from different countries and hospital centers.

Summary There is a great variability in the utilization of antiseptic agents, wound dressing types, and implementation of surgical debridement across the globe and different institutions. There is a lack of randomized controlled trials. However, the general principle is to protect the underlying viable exposed dermis, minimize the risk of infection, reduce the risk of pigmentary changes and scarring, and optimize the conditions for re-epithelization. Large-scale randomized clinical trials are needed for the optimization of wound care in these conditions.

Keywords Stevens-Johnson syndrome · Toxic epidermal necrolysis · Wound management · Wound dressing · Wound care

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are uncommon, acute, life-threatening mucocutaneous adverse reactions associated with a potentially high mortality rate. They are characterized by a cytokine-mediated keratinocyte cell death with resultant separation of the dermal-epidermal junction that leads to extensive detachment of the necrotic epidermis [1]. The incidence of SJS/TEN ranges from 1.4 to 9.2 cases per million person-year with a mortality rate that can exceed 30% [2–4].

SJS and TEN represent a spectrum of the same disease process being distinguished by the degree of body skin surface (BSA) affected by bullae and erosions. SJS is characterized by dusky erythema, atypical non-palpable targetoid lesions, vesicles, bullae, erosions, and epidermal detachment affecting < 10% of BSA. TEN is more extensive with epidermal detachment exceeding 30% [5]. SJS/TEN overlap represents involvement between 10 and 30% of BSA. Up to 95% of TEN cases are attributed to medications with allopurinol, sulfonamides, aminopenicillins, aromatic anticonvulsants, and non-steroidal anti-inflammatory drugs (NSAIDs) as common triggers. Up to 15% of cases may not be triggered by medications, and infectious etiologies such as mycoplasma pneumoniae have been implicated, particularly in children [1, 6–8].

Hsu et al. analyzed the Nationwide Inpatient Sample (NIS) from 2009 to 2012, which included approximately 20% of all US inpatient admissions. They determined that female gender and nonwhite race, particularly Asians and blacks, were associated with a higher incidence of SJS/TEN. Additionally, their study yielded a mean adjusted mortality of 4.8% for SJS, 19.4% for SJS/TEN, and 14.8% for TEN [2]. The authors also found the age older than 40 years, past medical history of one

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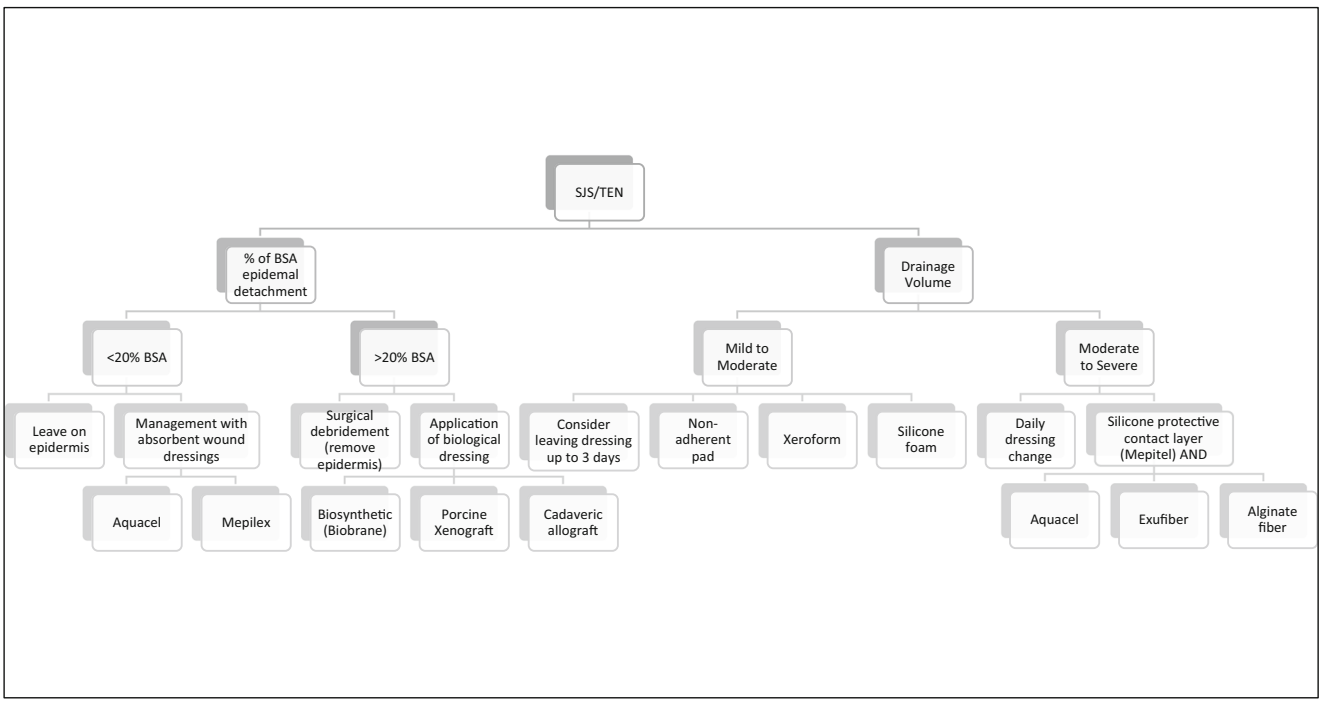
or more chronic conditions, hematological malignancy, and infections to be significant predictors of mortality in patients with SJS/TEN [2]. Sekula et al. found that mortality rates increased over time, with TEN patients reaching 1-year mortality rate of 49% [9].

In addition to promptly discontinuing the offending agent, supportive care and wound management are fundamental components of SJS/TEN management. A multidisciplinary approach with meticulous skin care with close attention to mucosal involvement including ocular and genital surfaces, fluid and electrolyte management, and nutritional support all play a significant role [10]. However, no standard approaches specific to wound management have been widely accepted and vary depending on the hospital center and its experience [10, 11]. In this manuscript, we will review the pathophysiology, clinical manifestations, and management of SJS/TEN, with the particular emphasis on the available and most recent published literature on the wound care management in the hospital setting.

Clinical Manifestations

The onset of mucocutaneous manifestations is typically preceded by a prodrome of fever, anorexia, myalgias, arthralgias, and malaise [4, 12]. The onset of symptoms generally ranges from 4 to 28 days after exposure to the culprit medication [13]. The spectrum of skin involvement ranges from poorly defined tender and painful dusky erythematous, violaceous macules and patches to vesicles, bullae, and erosions that typically affect the face, trunk, and extremities (Fig. 1). Atypical targetoid lesions characterized by non-palpable annular macules and patches with dusky centers can be observed (Fig. 2) [5]. In severe cases, progression to complete epidermal detachment can occur with involvement of significant BSA (Fig. 3). Application of pressure towards the edges of the bullae results in shedding of the epidermis from the underlying dermis of the adjacent skin, which is known as the positive Nikolsky sign [5].

Patients may also initially present with diffuse confluent erythema or a morbilliform eruption. The presence of fever



SJS, Steven Johnson's Syndrome; TEN, Toxic Epidermal Necrolysis; BSA, Body Surface Area

Fig. 1 Diffuse erythematous patches with necrotic dusky centers, vesicles and bullae. SJS Steven-Johnson syndrome, TEN toxic epidermal necrolysis, BSA body surface aarea. Suggested treatment algorithm for SJS/TEN wound care (suggested algorithm for wound care management as extrapolated from the available literature. Individual approaches vary widely depending on the hospital center and individual physician preference and experience). Wound care management of SJS/TEN patients should be based on the percentage of epidermal detachment and degree of exudate and signs of infection. In some burn centers, the threshold for the epidermal detachment has been established at 20% BSA, in which cases surgical debridements and biological dressings are utilized. In contrast, those with < 20% BSA involvement are managed with a conservative approach, specifically "leave on" epidermis and absorbent dressings. Exudate volume is another critical factor playing a role in the choice of wound dressings. Areas with mild to moderate exudate can be managed with less frequent dressing changes (i.e., every 3 days) and widely available wound dressings, such as non-adherent pads and bismuth tribromophenate petroleum dressings (e.g., Xeroform®). In contrast, regions with moderate-to-severe exudate require daily dressing changes, a protective contact layer (e.g., Mepitel® or Adaptic®), and a highly absorbent dressing such as gelling fibers (e.g., Aquacel®, Sorbion®, Exufiber®) or alginate fibers

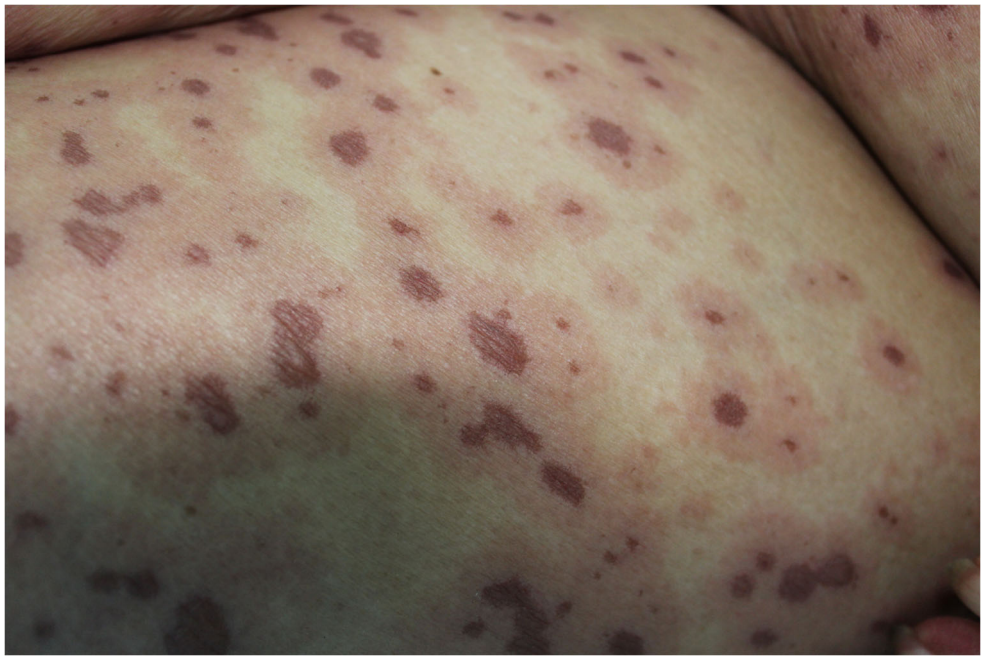


Fig. 2 Atypical targetoid lesions of SJS/TEN

and prodromal symptoms, skin tenderness, photophobia, eye symptoms, and pain with swallowing can serve as a clue to early and evolving SJS/TEN [5, 12] Greater than 90% of patients will develop mucosal involvement, which can present prior or subsequent to cutaneous symptoms (Fig. 4) [5]. Painful ulcerations of the mucosal surfaces including oral, pharyngeal, ocular, or genital surfaces with overlying hemorrhagic crusts will develop in virtually all cases of TEN [14]. Less commonly involvement of the trachea, bronchial tree, esophagus and GI tract can be seen [15]. Symptoms typically have an abrupt onset with rapid development and progression over 24–48 h [5].

Pathophysiology of SJS/TEN

The exact pathophysiology of SJS/TEN has not yet been elucidated; however, recent studies have broadened our understanding. The assertion that the disease process is driven by massive keratinocyte apoptosis has been generally accepted [16]. Culprit medications result in the clonal generation of

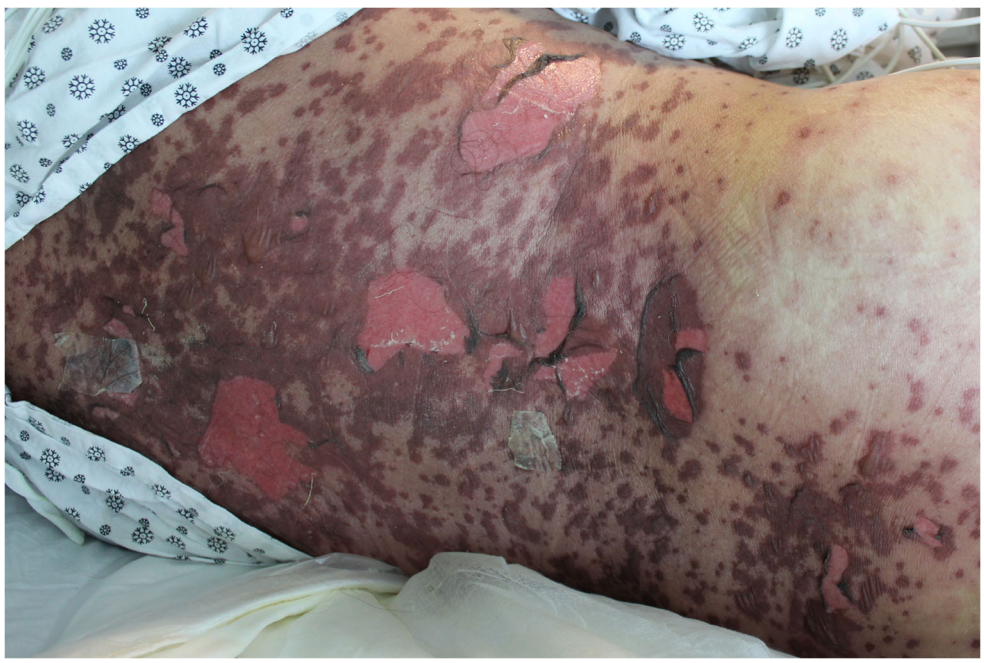


Fig. 3 Confluent areas of epidermal necrosis and detachment with epidermal sloughing on the back

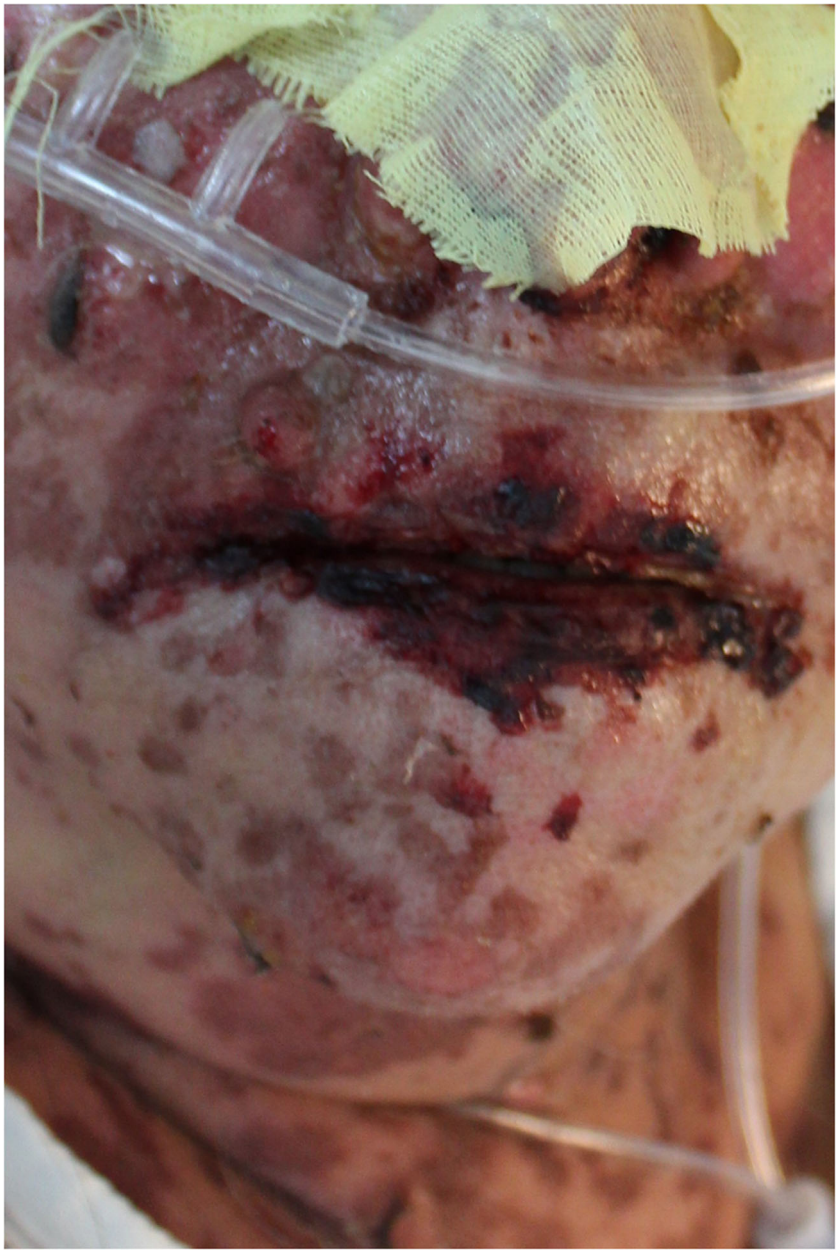


Fig. 4 Extensive and confluent hemorrhagic mucositis of the lip mucosa

drug-specific CD8-positive, MHC class I-restricted cytotoxic T-cells, with subsequent direct and indirect keratinocyte apoptosis mediated by cytokines, recruitment of inflammatory cells and soluble cell-death mediators [17, 18].

The main implicated cells mediating keratinocyte death include cytotoxic T-cells and natural killer (NK) cells [19, 20]. Multiple cytotoxic proteins and cytokines have been implicated in pathogenesis including perforin-granzyme pathway, Fas ligand, tumor necrosis factor (TNF), TNF-related apoptosis-inducing ligand (TRAIL), and granulysin [19, 21–27]. Granulysin is a protein that has been found in high concentration in blister fluid and serum of SJS/TEN patients [28]. Additionally, plasma levels have been correlated with disease severity and prognosis [28]. Drug-activated monocytes could secrete annexin A1, a protein highly associated with auto-immunity, and is typically elevated in patients with systemic lupus erythematosus [29]. Annexin A1 binds with formyl peptide receptor 1, with resultant necrosis of keratinocytes [30].

Medical Treatment

The clinical evolution of SJS/TEN is characterized by a rapidly progressive course. Thus, accurate and prompt intervention and management are of paramount importance [5]. Along with properly identifying and withdrawing the culprit agent, systemic medications are often utilized in an attempt to halt the progression and improve the time to re-epithelialization. However, there is a lack

of consensus and evidence-based data, and further rigorous studies are needed to improve our therapeutic armamentarium. Clinical trials of therapeutic interventions present a unique challenge given the rarity of the disease, variability of treatment protocols, and difficulties in enrolling patients. The choice of a specific agent may vary depending on the physicians' preference, training exposure and institutional experience and protocols [14]. Intravenous immunoglobulin (IVIG), systemic corticosteroids, cyclosporine, and tumor necrosis factor (TNF) inhibitors have all been used to a variable extent [14, 31•].

One rationale supporting the use of IVIG was based on its ability to target the Fas-ligand-induced apoptosis [32]. Multiple studies, mostly retrospective, have investigated its utility but with conflicting results [33–37]. Some retrospective studies reported a reduction in mortality when compared to predicted mortality using a validated prognostic score (SCORE of Toxic Epidermal Necrolysis, SCORTEN) [34, 37–40]. Additionally, Micheletti et al. recently published a multicenter retrospective study of 377 SJS/TEN reporting an observed improved mortality as compared to the SCORTEN-predicted Standardized Mortality Ratio among patients treated with IVIG as monotherapy or in combination with systemic corticosteroids [31•]. In contrast, Bachot et al. completed a prospective non-comparative clinical trial of IVIG on 34 patients without a reduction in mortality or prevention of progression of epidermal detachment [41].

There is conflicting and insufficient data on the utility of systemic corticosteroids. Older studies advised against their use, suggesting that they impeded wound healing, increased the risk of infections, and resulted in increased mortality [14, 42]. More recent studies have reported potential reduction in mortality, accentuating its potential benefit when combined with other medications (i.e., IVIG) [31•, 43, 44].

Wang et al. conducted a randomized clinical trial of etanercept versus corticosteroids for SJS/TEN patients, finding that both treatment arms had a lower than SCORTEN predicted mortality rate [45••]. Subgroup analysis showed a statistically significant superior skin healing outcomes in patients treated with etanercept with > 10% BSA [45••]. Lastly, cyclosporine has been utilized with an increased frequency [46, 47, 48•]. Valeyrie-Allanore et al. performed an open trial of cyclosporine as monotherapy in 29 consecutive patients with SJS/TEN and reported a 100% survival rate [46]. However, the patient population had a mean SCORTEN score of 1.27, which is relatively low compared to previous and original studies [46]. A retrospective study of 42 patients with SJS/TEN found a significant reduction in mortality when patients received cyclosporine (2/26 = 7.7%) compared to other treatments (IVIG or steroids, 5/16 = 31.3%) [48•].

General Approach to Wound Management

In addition to identification and discontinuation of the culprit medication when possible, wound care is a fundamental component of management. The general principle is to protect the underlying viable exposed dermis, minimize the risk of infection, reduce the risk of pigmentary changes and scarring, and optimize re-epithelization. Adequate wound care is critical to minimizing insensible losses and dehydration. Skin infections and septicemia are significant predictors of mortality in patients and facilitating the healing process may diminish its risks [2, 49]. In particular, infections with *Staphylococcal aureus* and *Pseudomas aeruginosa* can often complicate the clinical course [50, 51].

There is no gold standard or currently universally accepted guidelines for wound care in patients with SJS/TEN. Since it has been inadequately studied and there is sparse evidence-based data, healthcare providers usually emulate local burn guidelines and rely on expert opinions, which may vary depending on the hospital center [49•, 52, 53, 54, 55••]. This partly stems from the lack of randomized controlled studies that can support the guidelines for wound management of both pediatric and adult SJS/TEN patients [56••, 57••]. Additionally, there is often a lack of necessary details in wound care approaches reported in the literature. Some proposed protocols differ as much as calling for skin slough debridement and blister deroofing, while others utilize "no-touch" protocols and using a detached epidermis as a 'biologic dressing' [58, 59•].

In general, frequent wound dressing changes and patient manipulation, which can interfere with wound healing and re-epithelization, should be minimized [14, 50, 58, 60]. Furthermore, the use of "air-fluidized" or equivalent air mattresses is recommended to minimize the degree of injury to the epidermis [62•]. Irrigation of wounds and intact epidermis can be performed with warm sterile water, saline, or diluted chlorhexidine (1/5000). Frequent application of bland emollients such as petrolatum-based products is recommended to the entire cutaneous surface [56••, 58]. According to some guidelines, application of topical antimicrobial agents or silver-impregnated dressings is recommended only to areas of epidermal detachment [58]. Topical potent corticosteroid application to involved, erythematous but not detached skin can be considered [56••]. In the algorithm from Chelsea and Westminster Hospital Burns Service denuded areas are covered with Biobrane (Smith & Nephew Healthcare Ltd., Hull, UK), cryopreserved cadaveric allografts and/or E-Z derm (Molnlycke Health Care, US, LLC, Norcross, GA), a porcine-derived xenograft. An emollient is applied to normal skin, while topical corticosteroids are used to cover clinically erythematous skin [59•].

A wide range of dressings has been utilized including non-adherent, biological, biosynthetic, silver or antibiotic-

impregnated, nanocrystalline silver dressings, and collagen sheets. Biological dressings include allografts, xenografts, cultured human allogeneic and autologous epidermal sheets [49•]. As an example, UK guidelines suggest the use non-adherent dressings to areas of sloughed epidermis such as Mepitel®, a non-adherent contact layer, (Molnlycke Health Care, US, LLC, Norcross, GA), or Telfa™ a non-adherent gauze (Covidien, Mansfield, MA, USA) followed by secondary foam or absorptive dressings such as Exu-Dry (Smith & Nephew, London, UK) to accommodate the exudate [58]. For surgically debrided wounds biologic, allograft and xenograft dressings are typically used. However, overall there is a great variability in specific approaches and protocols across the United States and the world (Table 1).

Mahar et al. conducted a systematic review of SJS/TEN management and outcomes in various burn-unit centers. This was a large retrospective analysis of TEN patients treated over the span of more than 22 years involving 708 patients. It demonstrated great variability in the types of dressings used and debridement vs conservative no-touch approach. From the 20 studies that met the inclusion criteria, only 15 (75%) described their wound management regimens. Furthermore, 12 (80%) of these reported the use of any type of dressing, whereas 7 (46.6%) reported using dressings containing various antimicrobial products (i.e., silver-based dressings) [63]. Additionally, a very recent survey-based study of medical directors and co-directors of the American Burn Association (ABA)-verified burn centers demonstrated that only 61.3% of responders had an established protocol in place for SJS/TEN management [51]. Similarly, Hong-Gam Le et al. performed a phone interview study of nursing supervisors at 111 US burn centers. Only 27% of responders reported the existence of a written guideline and treatment protocol [64].

In the dermatological literature, a survey-based study of burn centers and Dermatology departments showed that only 54% had established management guidelines. Among these, 46% used their individual institutional approach, while 8% used the ABA proposed guidelines. While the response rate was only 25%, the most common topical treatment was silver-coated/silver-impregnated dressings (73%), semisynthetic/synthetic dressings (43%), topical antimicrobials (43%), and bioactive skin substitutes (38%) [65]. Another survey study of approach to infection control, wound care, and systemic treatment on SJS/TEN patients sent to 31 burn unit directors in the United Stated showed that only 61.3% of the units had an established protocol [65].

The Role of Debridement

There is insufficient data on the role of surgical debridement of vesicles, bullae, and detached epidermis and no universally accepted guidelines exist. Surgical debridement involves removal of detached epidermis followed by physiological wound closure using biosynthetic dressings, xenograft or allograft [58]. The use of debridement including daily dressing changes, whirlpool, and the use of biologic dressings has been utilized throughout US burn-unit centers [10]. Wound debridements are particularly necessary prior to the application of a skin substitute [66].

In contrast, an alternative approach involves aspiration of bullae and leaving the denuded epidermis in place, with use of appropriate irrigation, anti-septic agents and dressings [55••]. Aspiration of bullae fluid may theoretically remove the cytokines that propagate inflammation and keratinocyte necrosis and separation [59•]. The notion that the epidermis left "in place" can serve as a biologic dressing has created an alternative anti-shear treatment approach [10, 67]. A retrospective review from a burn-unit in Chicago over 20 years demonstrated that such approach resulted in a reduction in mortality of 42% for patients with a SCORTEN score of 3 or less as compared with expected mortality. In contrast, no impact on mortality was observed among patients with a SCORTEN score of 3 or higher. Overall mortality was 27%, an improvement based on the SCORTEN-predicted mortality of 30.2%, with resultant 11% reduction in predicted mortality. However, this was not statistically significant given an overall low number of patients [10]. The authors proposed that this may be an alternative approach with equivalent mortality that can diminish the utilization of resources and pain associated with frequent dressing changes. The proposed algorithm used in the Chelsea and Westminster Hospital Burns Service in London similarly did not use debridement and instead involved aspiration of bullae, Mepitel (Molnlycke Health Care, US, LLC, Norcross, GA) and betadine soaked gauze [59•]. All of the patients had TEN with predicted mortality exceeding 80% but there was no observed mortality.

On the other hand, another comparable retrospective analysis from the university associated burn-unit center in Seattle, Washinton demonstrated that debridement approach involving the removal of sloughed epidermis and dermal protection with porcine xenograft resulted in a relative reduction in mortality of 33% ($P = 0.011$). All loose skin and blisters were removed with warm saline or sterile water-soaked washcloths without detergent in the operating room with subsequent placement of a Porcine xenograft [68]. Two separate studies from California and UK utilizing a debridement approach reported an overall mortality rate of approximately 10%, an improvement when compared to expected mortality [55••, 69••]. Linford et al. shared the approach used in the Helsinki Burn Center, which involves gentle manual debridement of any detached epidermis and wound irrigation with subsequent application of the skin substitute Suprathel (PolyMedics Innovations, Filderstadt Germany) to areas of sloughed epidermis, which can be covered with Mepitel One (Monlycke Health Care, Gothenburg, Sweden). Its proposed advantages are ease of application, fixing, reduction in pain and low risk of infection [70, 71].

Table 1 Wound care management in SJS/TEN. Adapted with permission [61]

Type	Brands	Composition	Proposed mechanism of action	Advantage	Disadvantage
Topicals					
Sterile water/saline	N/A	N/A	Skin irrigation to clean wounds	Very inexpensive and readily available	Lack of antimicrobial properties. Saline can interfere with some silver containing dressings
Chlorhexidine	Betasept® Purdue Products L.P., Stamford, CT, USA	N/A	Antiseptic	Inexpensive; easily applied in large surfaces	Abundant irrigation required
Silver sulfadiazine	Silvadene® Pfizer. New York, NY USA	N/A	Silver as antimicrobial	Silver decreases risk of infection; prevents dressing adhesion; inexpensive	Potential risk of systemic silver absorption
Povidone-iodine	Betadine® Betadine. Stamford, CT USA	N/A	Antimicrobial agent	Decreases risk of infection; might reduce overall healing time in burn wounds; inexpensive	Risk of iodine cytotoxicity
Petroleum jelly	Vaseline® Unilever, USA	N/A	Wound and skin hydration	Maintains wound/skin hydration; inexpensive	Spray preparations preferred as skin rubbing should be avoided
Corticosteroid ointment	N/A	N/A	Reduction of cutaneous inflammatory changes	Potential faster healing and pain reduction	Lack of sufficient data of efficacy in SJS/TEN. Potential increase risk of infection; risk of systemic absorption
Dressings					
Synthetic					
Silicone	Mepitel® Molnlycke Health Care, US, LLC, Norcross, GA	Gentle two-sided silicone dressing	Contact layer to protect the wound and surrounding skin	Mesh structure permeable to exudate; adheres to wound edge but not to wound bed; easy to apply	Costly; requires a secondary dressing on top
Biosynthetic	Biobrane, Smith&Nephe-w, Ontario, Canada	Silicone membrane bonded to a nylon mesh; embedded with porcine collagen peptides	Assumes the role of epidermis by maintaining moist environment without accumulating exudate	One-time application; transparent	Costly; only used for wounds with large surface area
Other	Suprathel, PolyMedics Innovations, Denkendorf, Germany	Thin microporous membrane	Stimulates angiogenesis and wound healing; acidification decreases bacterial growth	One-time application; transparent	Costly
Fiber					
Silver-impregnated	Acticoat, Smith & Nephew, Ontario, Canada	Nanocrystalline silver impregnated dressing	Nonadherent, absorbent wound dressing that helps to maintain a moist	Silver decreases risk of infections, modulates matrix metalloproteinases, and promotes	Conflicting evidence regarding silver cytotoxicity in vitro and potential risk of systemic silver absorption in patients with

Table 1 (continued)

Type	Brands	Composition	Proposed mechanism of action	Advantage	Disadvantage
			environment at the wound surface	neovascularization, which may result in faster wound healing; fewer dressing changes	involvement of large surface areas; costly
	Aquacel Ag, Convatec, Bridgewater, NJ	Hydrofiber embedded with silver ions	Nonadherent, absorbent wound dressing that helps to maintain a moist environment at the wound surface	Silver decreases risk of infections; fewer dressing changes; very gentle, removal with virtually no trauma	Conflicting evidence regarding silver cytotoxicity in vitro and potential risk of systemic silver absorption in patients with involvement of large surface areas; costly
Crystalline cellulose	Veloderm, BTS srl, Ancona Italy	Cellulose microfibrils	N/A	Decreased dressing changes	Costly
Alginate fiber		Nonwoven fibers derived from seaweed		Cooling effect; easy application; calcium ions can be homeostatic	Becomes a gel that can be messy; works only with exudative wounds, not with dry wounds
Biologic					
Porcine xenograft	E-Z derm, Molnlycke Health Care, US, LLC, Norcross, GA	Porcine epidermis and dermis with collagen and growth factors	Serves as natural barrier for replacement of damaged skin	Abundant; inexpensive; histologically similar to human skin	Opaque; epidermis underneath cannot be visualized
Cadaveric allograft	Theraskin, Solsys Medical, Newport News, VA	Human epidermis and dermis with collagen and growth factors	Natural barrier; stimulate wound healing	Provides human-derived factors and cytokines	Opaque; epidermis underneath cannot be visualized; costly; limited availability
Other					
Foam	Mepilex® Molnlycke Health Care, US, LLC, Norcross, GA (± Ag)	Absorbent foam dressing	Wound barrier; absorb drainage; gentle adhesion	Highly absorbent; prevent infection (+ Ag); low trauma at dressing change; can stay for multiple days	Costly
Non-adherent pad	Telfa™ Covidien, Mansfield, MA, USA	Cotton gauze with non-adherent film	Wound barrier; absorb drainage	Very inexpensive and widely available	Not very absorbent; requires frequent changes
Bismuth tribromophenate--impregnated gauze	Xeroform® Sherwood Medical, St. Louis, MO, USA	Petrolatum mesh gauze with bismuth tribromophenate	Bismuth tribromophenate as antimicrobial	Inexpensive; widely available	Requires frequent changes; requires absorbent dressing on top

N/A not applicable, *Ag* silver

Studies have reflected this variable approach to management in the literature. A recent retrospective analysis of SJS/TEN patients in a Canadian burn unit from 2001 to 2011 found that bullae were debrided in 44% of patients with TEN, 14% of patients with SJS/TEN and 7% of patients with SJS [49•]. Canadian and US-based survey study of burn centers and Dermatology departments demonstrated that 62% of centers' directors implemented early debridement of nonviable tissue [65]. Similarly, in a retrospective analysis of patients treated in university-based burn units in California all patients underwent wound debridement [69••]. In the retrospective study from UK from 2004 to 2016, all patients underwent wound care protocol involving debridement of detached epidermis using betadine/chlorhexidine and gauze debridement within 48 h of symptoms onset, followed by dermal irrigation with betadine or chlorhexidine [55••]. For those patients presenting 2–5 days after onset of symptoms, Versajet TM (Smith and Nephew Medical Ltd., Memphis TN, USA) was utilized. For those patients presenting less than 2 days following the onset of disease with non-infected and extensive areas of epidermal sloughing, Biobrane (Smith & Nephew) was used for wound coverage. In contrast, allograft was used for closure in those with greater than 5 days of symptoms. In cases of skin infection or limited areas of involvement, silver-based/non-adherent dressings were used [55••]. Versajet™ Hydrosurgery System (Smith and Nephew Medical Ltd., Memphis TN, USA) is a gentle wound debridement tool frequently utilized in burn patients [72]. In management of SJS/TEN, blisters and involved epidermis are gently debrided without excision of the underlying healthy dermis. This device has shown similar burn debridement and quality of healing outcomes compared to conventional escharotomy, but with considerably easier and faster procedures [72–74].

There is no clear consensus on the role of surgical wound debridement in patients with SJS/TEN. While, the recent guidelines proposed by the British Association of Dermatologists for children under the age of 18 discuss both the conservative and debridement approaches, the strength of recommendations based on the available evidence, expert opinion, and consensus appears to be stronger for debridement. They do, however, advocate an initial conservative approach followed by utilization of debridement under general anesthesia with wound closure using a biosynthetic dressing only in the case of disease progression including epidermal detachment, infection, delayed healing, and involvement of dermis [56••]. Similarly, the UK guidelines for management of SJS/TEN in adults recommend initial conservative management. Subsequently, manual surgical debridement or using a Versajet TM (Drytac, Bristol, UK) can be added in cases of progression and extensive involvement (> 30% BSA) followed by application of Biobrane (Smith & Nephew)/allograft/xenograft skin in patients with early presentation and large confluent non-infected areas [57••]. The proposed management guidelines published by the ABA in 2008 suggested debridement of denuded epidermis but did discuss an alternative approach of using the epidermis as a biologic dressing and the conservative approach to wound care [50]. In contrast, proposed guidelines from France do not recommend removal of detached epidermis [62•].

Wound Dressings

Numerous dressings have been used to remove or prevent the formation of biofilm, diminish the risk of infection, and optimize wound healing environment and re-epithelization [10, 14, 54, 75, 76]. The ideal dressing should be able to cover all areas of epidermal sloughing, be sufficiently absorbent to remain attached for multiple days, have non-adherent properties to minimize trauma during exchanges and be able to prevent infection and biofilm formation. The goal of wound care in SJS/TEN is to minimize physical manipulation of the patient, which may cause more epidermal sloughing and pain, and reduce the frequency of dressing changes while attempting to mitigate the risk of infection. Evidence is lacking on treatments and there is wide variability in the choice of wound dressings and anti-microbial agents. Petrolatum containing gauzes or other non-adherent dressings can be utilized by themselves or in combination with advanced dressings depending on the severity of involvement and availability [62•]. Petrolatum gauzes maintain hydration in the wound and act as a physical barrier to prevent bacteria colonization. However, these dressings can dry and traumatize the skin when removed. Furthermore, they need to be changed daily [54]. Dressings such as bismuth tribromophenate and petrolatum-impregnated mesh gauze (Xeroform®, Sherwood Medical, St. Louis, MO) can be used to cover denuded areas of epidermis with or without antibacterial or antimicrobial ointments [10].

Among anti-septic topical medications, 0.5% silver nitrate solution and silver sulfadiazine cream (Silvadene, Monarch Pharmaceuticals, Bristol, TN) have been used but require frequent dressing changes [77]. Some of the drawbacks of silver sulfadiazine application is potential skin irritation and pseudoeschar formation. Additionally, released silver ions can be de-activated by wound exudate [78]. A recent survey of US burn unit directors demonstrated that greater than 50% of the burn units applied topical antibiotics to denuded skin (58%) and chlorhexidine rinses to the mouth (51.6%), utilized whirlpool baths (12.9%), topical corticosteroids (6.5%), and diluted hydrogen peroxide oral cavity rinse (3.2%) [51]. Areas of denudation were irrigated utilizing dilute chlorhexidine (51.6%), water (22.6%), and saline (12.9%). A large retrospective analysis of 15 burn centers in the USA from 1995 to 2000 demonstrated the use of these interventions: silver nitrate solution (14.3%), bacitracin (20%), Xeroform® (7.9%; Sherwood Medical, St. Louis, MO), and silver

sulfadiazine (9.6%) as well as biological dressings such as xenograft (6.8%), allograft (2%), Biobrane® (11.5%; Dow B. Hickam, Inc., Sugarland, TX), and Acticoat® (12.6%; Westaim Biomedical, Alberta, Canada) [79]. A more recent survey-based study of US-based burn centers demonstrated that the most common wound dressing used were Mepilex Ag® (Mölnlycke Health Care US, LLC, Norcross, GA) (48.4%), followed by biological skin substitutes (45.2%), Acticoat® (Smith and Nephew, Ft. Saskatchewan, Canada) (32.3%), petrolatum gauze (29.0%), TheraBond® 3D, Bacitracin, N-Terface ® (22.6%), silver sulfadiazine (12.9%), and TELFA™ (6.5%) [51]. There was no consensus on the frequency of dressing changes, ranging from daily, to every 3rd day to weekly depending on the dressing type. It should be noted that in this particular study the rate of responders was only 48%. Similarly, a recent retrospective analysis of SJS/TEN patients in a burn unit in Vancouver, Canada, demonstrated significant variability of dressing types: saline-soaked gauze (22%), dressings containing antibiotics (17%), silver sulfadiazine (14%), steroid containing dressing (15%), vaseline gauze (14%), and silicone coated dressing (7%) [49]. A retrospective study over 15 years in two California-based burn units showed the use of antimicrobial, silver releasing dressing (Acticoat, Smith and Nephew) between 2000 and 2011 and Exsalt (Exciton Technologies) between 2012 and 2014. Exsalt dressing was covered with gauze and irrigated every 6 h. Dressing changes occurred every 3 days. Utilizing this wound care approach their estimated overall mortality rate was 10% [69••].

The introduction and increased availability of more advanced silver-impregnated or coated dressings have allowed for sustained release of silver ions and the reduction of frequent dressing changes [10, 77, 80]. Silver anti-microbial properties stem from its interference with electron transport and DNA binding and inhibition of replication [78]. Mepilex is a highly absorbent foam dressing, which contains a special contact layer to minimize pain and trauma during dressing changes. The highly absorbent property allows for less frequent dressing changes. Mepilex Ag contains silver, which provides antiseptic and antimicrobial properties. It has been used in wound care since the 1960s, and its use has resulted in a reduction in wound infections, wound exudate volume, and in some cases wound healing time [81]. Silver impregnated or coated dressings can provide broad-spectrum anti-microbial coverage and reduce the need for frequent dressing changes [77]. On the other hand, high concentrations of silver could be cytotoxic and impede wound healing [82]. Additionally, the use of impregnated silver dressings in SJS/TEN with extensive BSA involvement has potential risk of systemic silver absorption, which can result in symptoms of argyria [83].

Aquacel Ag (ConvaTec, Skillman, NJ) is an absorbent silver-impregnated hydrofiber dressing with gel forming ability designated for highly exudative wounds. These dressings can be used as contact layers but, due to their lack of adhesive, maintaining them in place could represent a challenge. Acticoat is a nanocrystalline silver-impregnated gauze dressing. Compared to silver nitrate solution dressings, nanocrystalline silver dressings have shown a reduction in the frequency of dressing changes in chronic wounds and reduction of skin infection in burn patients [81, 84, 85]. The two-layer construction of Acticoat creates moist environment and results in reduced de-activation of silver ions that are released at a sustained rate [78]. Silver nitrate crystalline dressings, such as Acticoat need to be kept wet with a minimal amount of sterile water to result in release of silver ions. Wetting with sterile saline should be avoided, which results in precipitation of silver as silver chloride with subsequent loss of antimicrobial properties [75, 77]. Nanocrystalline silver-coated dressings stay attached for 3 days, while secondary dressings, for which wrap gauze, non-adhering dressing, or burn pads can be utilized, can be changed on a daily basis [75]. This approach to wound care in SJS/TEN patients, along with debridement of non-viable tissue during dressing changes, has been reported to reduce the rate of secondary infections and the time to full re-epithelization [75].

There are emerging novel wound dressings that have not yet been investigated for the use in SJS/TEN but could potentially serve as alterative approaches in the future. Dialkylcarbomoyl Chloride (DACC)-coated dressings (Cutimed® Sorbact®, BSN Medical, Hamburg, Germany) have antimicrobial properties that prompted their use in chronic and surgical site wounds [86]. The DACC coating creates a strong hydrophobic charge that has shown to irreversibly bind to bacteria. Given that the dressing has no chemically active substances and aims to remove and not destroy bacteria, it presents potential advantages, including no bacterial resistance, no cytotoxicity, and no bacterial endotoxin release [86, 87]. Similarly, dressings containing copper oxide have recently emerged as an alternative to long-time used silver dressings. Some researchers denote that copper is an essential trace element that not only has biocidal properties but also has a crucial role in skin regeneration and angiogenesis [88, 89]. The use of concentrated surfactants in the management of wounds is an emergent concept, and the use of such products to soften, loosen, and trap debris is gaining acceptance [90]. Concentrated surfactant gels are biocompatible and have shown protection against biofilm formation [91]. PluroGel® (Medline, Northfield, Illinois) is a water-soluble, surfactant-based wound dressing that develops a moist wound healing environment protecting the surrounding healthy tissue and softening wound debris [90]. Application of these types of dressings and especially their efficacy has yet to be investigated in SJS/TEN.

Biological dressings or biological skin substitutes include porcine xenograft, cadaveric allograft, and biosynthetic silicone dressings. These dressings may be placed to cover

denuded areas and following the debridement of the devitalized epidermis. The porcine xenograft is composed of porcine epidermis and dermis, including collagen and growth factors. Its histological similarity to human skin, availability, and low price make it more accessible for use [54]. A retrospective study of 8 SJS/TEN patients with > 20% BSA involvement, where porcine xenograft was utilized, showed a reduction in pain scores and the use of pain medications when compared to a historic control [92•]. Cadaveric allografts are composed of human epidermis and dermis with growth factors and collagen. Compared to porcine xenograft, the cadaveric allograft provides human-derived factors and cytokines and has improved compatibility and successful placement. However, it is more expensive and not as readily available [54]. Application of allograft/xenograft to exposed dermis may logistically be challenging and requires general anesthesia. Its use has been shown to reduce the inflammatory response and facilitate healing [59•]. Its successful application depends on the ease of adherence to the underlying dermis, which can be affected by wound exudate, bacterial colonization, infection and shearing forces [59•]. In order to increase the grafts' efficacy, wound debridement should be considered for wound bed preparation [93]. Heimbach et al. published a retrospective review showing reduction in mortality as compared to historical data with utilization of biologic dressings [94]. Multiple reports describe successful application of allograft in the literature, but these are limited to case reports and series [95, 96]. Because SJS/TEN patients are critically ill, the use of autologous skin grafts should be avoided. The creation of a new donor site wound could potentially complicate the course of the hospitalization and create additional source of infection and complications.

Biologics dressing covering areas of epidermal detachment may remain in place for 1–2 weeks allowing to minimize the extent of manipulation and primary dressing changes [60]. Its use can reduce the loss of fluid up to 90% as compared to unprotected, open wound [97]. Biobrane (Smith & Nephew, Ontario, Canada) is a biosynthetic substitute composed of a layer of porcine collagen surrounded by a silicone membrane bonded by nylon mesh. This dressing provides permeable and elastic skin cover that acts as barriers for infections and helps control pain [98]. A retrospective study of 14 TEN patients who underwent surgical debridement found that Biobrane resulted in significant reduction of pain (2.9 vs 5.5, $p < 0.05$), earlier mobilization (walking at 3 days vs 7 days, $p = 0.003$), and quicker re-epithelialization (12.5 versus 16 days) as compared to patients in whom daily dressing changes using Lavasept antiseptic solution (Fresenius Kabi AG, Bad Homburg, Germany) and paraffin gauze were utilized [11]. Another retrospective study compared the use of Biobrane to other dressings including silver-based dressings such as Acticoat, Aquacel Ag (ConvaTec, Greensboro NC, USA), Silverlon (Argentum Medical Cura Surgical, Geneva, Il USA), greasy tulle gauze and open management with polysporin or vaseline application [76]. While the use of Biobrane was not associated with a change in a median time to wound healing, it was used in management of extensive BSA involvement and was not associated with infection. Multiple reports have shown successful utilization of Biobrane in patients with TEN but data are limited to case reports and series [97–99]. The use of Biobrane dressings in patients with TEN was associated with reduction of associated pain, improved re-epithelization, diminished risk of secondary infection, and improved mobilization. In cases of delayed patient presentation, the use of Biobrane may result in increased risk of infection, and thus allograft placement is preferred [55••]. Biobrane is also typically used in areas of extensive and confluent involvement and can be covered by secondary dressings such as betadine gauze to prevent shear.

Guidelines put forth by the ABA for the types of wound dressings list biosynthetic dressing Biobrane (Bertek Pharmaceuticals, Research Triangle Park, NC), biologic dressings, including porcine xenograft and cryopreserved human allograft, and Silver-impregnated dressings, such as the nanocrystalline silver dressing Acticoat (Smith & Nephew, Largo, FL) [50]. Frequent dressing changes with topical antimicrobial ointments or solutions are not recommended.

Conclusion

SJS and TEN are complex diseases that require a multidisciplinary approach and management. A wide range of dressing types and anti-microbial agents are used across the globe, and there are differences in the implementation of surgical debridements. Overall, there is a lack of evidence to universally validate any specific type of wound care management for SJS/TEN patients. Further multicenter interventional and comparison trials are needed for an improved and optimized evidenced-based approach to these catastrophic conditions.

Compliance with Ethical Standards

Conflict of Interest None.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Hotzenecker W, Prins C, French LE. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. In: Bolognia JL, Jorizzo JL, Schaffer JV, editors. Dermatology (Basel, Switzerland). Philadelphia: Elsevier Saunders; 2018. p. 332–47.
2. Hsu DY, Brieva J, Silverberg NB, Silverberg JI. Morbidity and mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis in United States adults. J Invest Dermatol. 2016;136(7):1387–97.
3. Frey N, Jossi J, Bodmer M, Bircher A, Jick SS, Meier CR, et al. The epidemiology of Stevens-Johnson syndrome and toxic epidermal necrolysis in the UK. J Invest Dermatol. 2017;137(6):1240–7.
4. Downey A, Jackson C, Harun N, Cooper A. Toxic epidermal necrolysis: review of pathogenesis and management. J Am Acad Dermatol. 2012;66(6):995–1003.
5. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part I. Introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis. J Am Acad Dermatol. 2013;69(2):173.e1–13 quiz 85-6.
6. Wetter DA, Camilleri MJ. Clinical, etiologic, and histopathologic features of Stevens-Johnson syndrome during an 8-year period at Mayo Clinic. Mayo Clin Proc. 2010;85(2):131–8.
7. Ferrandiz-Pulido C, Garcia-Patos V. A review of causes of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. Arch Dis Child. 2013;98(12):998–1003.
8. Sassolas B, Haddad C, Mockenhaupt M, Dunant A, Liss Y, Bork K, et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis: comparison with case-control analysis. Clin Pharmacol Ther. 2010;88(1):60–8.
9. Sekula P, Dunant A, Mockenhaupt M, Naldi L, Bouwes Bavinck JN, Halevy S, et al. Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. J Invest Dermatol. 2013;133(5):1197–204.
10. Dorafshar AH, Dickie SR, Cohn AB, Aycock JK, O'Connor A, Tung A, et al. Antishear therapy for toxic epidermal necrolysis: an alternative treatment approach. Plast Reconstr Surg. 2008;122(1):154–60.
11. Boorboor P, Vogt PM, Bechara FG, Alkandari Q, Aust M, Gohritz A, et al. Toxic epidermal necrolysis: use of Biobrane or skin coverage reduces pain, improves mobilisation and decreases infection in elderly patients. Burns. 2008;34(4):487–92.
12. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med. 1994;331(19):1272–85.
13. Duong TA, Valeyrie-Allanore L, Wolkenstein P, Chosidow O. Severe cutaneous adverse reactions to drugs. Lancet (London, England). 2017;390(10106):1996–2011.
14. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part II. Prognosis, sequelae, diagnosis, differential diagnosis, prevention, and treatment. J Am Acad Dermatol. 2013;69(2):187.e1–16 quiz 203-4.
15. de Prost N, Mekontso-Dessap A, Valeyrie-Allanore L, Van Nhieu JT, Duong TA, Chosidow O, et al. Acute respiratory failure in patients with toxic epidermal necrolysis: clinical features and factors associated with mechanical ventilation. Crit Care Med. 2014;42(1):118–28.
16. Heng YK, Lee HY, Roujeau JC. Epidermal necrolysis: 60 years of errors and advances. Br J Dermatol. 2015;173(5):1250–4.
17. Roujeau JC, Bricard G, Nicolas JF. Drug-induced epidermal necrolysis: important new piece to end the puzzle. J Allergy Clin Immunol. 2011;128(6):1277–8.
18. Ko TM, Chung WH, Wei CY, Shih HY, Chen JK, Lin CH, et al. Shared and restricted T-cell receptor use is crucial for carbamazepine-induced Stevens-Johnson syndrome. J Allergy Clin Immunol. 2011;128(6):1266–76.e11.
19. Nassif A, Bensussan A, Boumsell L, Deniaud A, Moslehi H, Wolkenstein P, et al. Toxic epidermal necrolysis: effector cells are drug-specific cytotoxic T cells. J Allergy Clin Immunol. 2004;114(5):1209–15.
20. Morel E, Escamochero S, Cabanas R, Diaz R, Fiandor A, Bellon T. CD94/NKG2C is a killer effector molecule in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. J Allergy Clin Immunol. 2010;125(3):703–10 10.e1–10.e8.
21. Tohyama M, Hashimoto K. Immunological mechanisms of epidermal damage in toxic epidermal necrolysis. Curr Opin Allergy Clin Immunol. 2012;12(4):376–82.
22. Paul C, Wolkenstein P, Adle H, Wechsler J, Garchon HJ, Revuz J, et al. Apoptosis as a mechanism of keratinocyte death in toxic epidermal necrolysis. Br J Dermatol. 1996;134(4):710–4.
23. Chung WH, Hung SI, Yang JY, Su SC, Huang SP, Wei CY, et al. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. Nat Med. 2008;14(12):1343–50.
24. Abe R, Yoshioka N, Murata J, Fujita Y, Shimizu H. Granulysin as a marker for early diagnosis of the Stevens-Johnson syndrome. Ann Intern Med. 2009;151(7):514–5.
25. Nassif A, Moslehi H, Le Gouvello S, Bagot M, Lyonnet L, Michel L, et al. Evaluation of the potential role of cytokines in toxic epidermal necrolysis. J Invest Dermatol. 2004;123(5):850–5.
26. de Araujo E, Dessirier V, Lapree G, Valeyrie-Allanore L, Ortonne N, Stathopoulos EN, et al. Death ligand TRAIL, secreted by CD1a+ and CD14+ cells in blister fluids, is involved in killing keratinocytes in toxic epidermal necrolysis. Exp Dermatol. 2011;20(2):107–12.
27. Mor G, Straszewski S, Kamsteeg M. The Fas/FasL system in reproduction: survival and apoptosis. TheScientificWorldJournal. 2002;2:1828–42.
28. White KD, Abe R, Ardern-Jones M, Beachkofsky T, Bouchard C, Carleton B, et al. SJS/TEN 2017: building multidisciplinary networks to drive science and translation. J Allergy Clin Immunol Pract. 2018;6(1):38–69.
29. Bruschi M, Petretto A, Vaglio A, Santucci L, Candiano G, Ghiggeri GM. Annexin A1 and autoimmunity: from basic science to clinical applications. Int J Mol Sci. 2018;19(5).
30. Saito N, Qiao H, Yanagi T, Shinkuma S, Nishimura K, Suto A, et al. An annexin A1-FPR1 interaction contributes to necroptosis of keratinocytes in severe cutaneous adverse drug reactions. Sci Transl Med. 2014;6(245):245ra95.
31. • Micheletti RG, Chiesa-Fuxench Z, Noe MH, Stephen S, Aleshin M, Agarwal A, et al. Stevens-Johnson syndrome/toxic epidermal necrolysis: a multicenter retrospective study of 377 adult patients from the United States. J Invest Dermatol. 2018;138(11):2315–21 **Largest cohort of US SJS/TEN patients. Presents valuable epidemiologic data, such as mortality rates and different treatment approaches in 18 US academic medical centers.**
32. Roujeau JC. Treatment of severe drug eruptions. J Dermatol. 1999;26(11):718–22.
33. Campione E, Marulli GC, Carrozzo AM, Chimenti MS, Costanzo A, Bianchi L. High-dose intravenous immunoglobulin for severe drug reactions: efficacy in toxic epidermal necrolysis. Acta Derm Venereol. 2003;83(6):430–2.
34. Chen J, Wang B, Zeng Y, Xu H. High-dose intravenous immunoglobulins in the treatment of Stevens-Johnson syndrome and toxic

epidermal necrolysis in Chinese patients: a retrospective study of 82 cases. Eur J Dermatol. 2010;20(6):743–7.
35. Kim KJ, Lee DP, Suh HS, Lee MW, Choi JH, Moon KC, et al. Toxic epidermal necrolysis: analysis of clinical course and SCORTEN-based comparison of mortality rate and treatment modalities in Korean patients. Acta Derm Venereol. 2005;85(6):497–502.
36. Stella M, Clemente A, Bollero D, Risso D, Dalmasso P. Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS): experience with high-dose intravenous immunoglobulins and topical conservative approach. A retrospective analysis. Burns. 2007;33(4):452–9.
37. Trent JT, Kirsner RS, Romanelli P, Kerdel FA. Analysis of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis using SCORTEN: the University of Miami experience. Arch Dermatol. 2003;139(1):39–43.
38. Rajaratnam R, Mann C, Balasubramaniam P, Marsden JR, Taibjee SM, Shah F, et al. Toxic epidermal necrolysis: retrospective analysis of 21 consecutive cases managed at a tertiary centre. Clin Exp Dermatol. 2010;35(8):853–62.
39. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol. 2000;115(2):149–53.
40. Cartotto R, Mayich M, Nickerson D, Gomez M. SCORTEN accurately predicts mortality among toxic epidermal necrolysis patients treated in a burn center. J Burn Care Res. 2008;29(1):141–6.
41. Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. Arch Dermatol. 2003;139(1):33–6.
42. Halebian PH, Corder VJ, Madden MR, Finklestein JL, Shires GT. Improved burn center survival of patients with toxic epidermal necrolysis managed without corticosteroids. Ann Surg. 1986;204(5):503–12.
43. Law EH, Leung M. Corticosteroids in Stevens-Johnson syndrome/toxic epidermal necrolysis: current evidence and implications for future research. Ann Pharmacother. 2015;49(3):335–42.
44. Schneck J, Fagot JP, Sekula P, Sassolas B, Roujeau JC, Mockenhaupt M. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: a retrospective study on patients included in the prospective EuroSCAR Study. J Am Acad Dermatol. 2008;58(1):33–40.
45.•• Wang CW, Yang LY, Chen CB, Ho HC, Hung SI, Yang CH, et al. Randomized, controlled trial of TNF-alpha antagonist in CTL-mediated severe cutaneous adverse reactions. J Clin Invest. 2018;128(3):985–96 **Features as one of the few randomized controlled trials in SJS/TEN. Reveals the superiority, in terms of mortality rate reduction, of etanercept compared to systemic corticosteroids.**
46. Valeyrie-Allanore L, Wolkenstein P, Brochard L, Ortonne N, Maitre B, Revuz J, et al. Open trial of ciclosporin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol. 2010;163(4):847–53.
47. Kirchhof MG, Miliszewski MA, Sikora S, Papp A, Dutz JP. Retrospective review of Stevens-Johnson syndrome/toxic epidermal necrolysis treatment comparing intravenous immunoglobulin with cyclosporine. J Am Acad Dermatol. 2014;71(5):941–7.
48.• Gonzalez-Herrada C, Rodriguez-Martin S, Cachafeiro L, Lerma V, Gonzalez O, Lorente JA, et al. Cyclosporine use in epidermal necrolysis is associated with an important mortality reduction: evidence from three different approaches. J Invest Dermatol. 2017;137(10):2092–100 **Clinical trial of cyclosporine compared to other therapies including IVIG and systemic steroids for the treatment of SJS/TEN. Although not a randomized study, this trial presents significant evidence supporting better mortality outcomes with the use of cyclosporine.**
49.• Papp A, Sikora S, Evans M, Song D, Kirchhof M, Miliszewski M, et al. Treatment of toxic epidermal necrolysis by a multidisciplinary team. A review of literature and treatment results. Burns. 2018;44(4):807–15 **Cohort of 67 single-center patients from a Hospital in Canada. Provides quantitative data on SJS/TEN triggers, length of stay, wound dressings, complications, and mortality. Helpful educational tool for healthcare providers.**
50. Endorf FW, Cancio LC, Gibran NS. Toxic epidermal necrolysis clinical guidelines. J Burn Care Res. 2008;29(5):706–12.
51. Richard EB, Hamer D, Musso MW, Short T, O'Neal HR Jr. Variability in management of patients with SJS/TEN: a survey of burn unit directors. J Burn Care Res. 2018;39(4):585–92.
52. Ying S, Ho W, Chan HH. Toxic epidermal necrolysis: 10 years experience of a burns Centre in Hong Kong. Burns. 2001;27(4):372–5.
53. Atiyeh BS, Dham R, Yassin MF, El-Musa KA. Treatment of toxic epidermal necrolysis with moisture-retentive ointment: a case report and review of the literature. Dermatol Surg. 2003;29(2):185–8.
54. Castillo B, Vera N, Ortega-Loayza AG, Seminario-Vidal L. Wound care for Stevens-Johnson syndrome and toxic epidermal necrolysis. J Am Acad Dermatol. 2018;79(4):764–7.e1.
55.•• Nizamoglu M, Ward JA, Frew Q, Gerrish H, Martin N, Shaw A, et al. Improving mortality outcomes of Stevens Johnson syndrome/toxic epidermal necrolysis: a regional burns centre experience. Burns. 2018;44(3):603–11 **Retrospective review of SJS/TEN patients in a burns center in the UK. Provides an in-depth analysis of the debridement alternatives and their role in the management of SJS/TEN patients. Also, presents a literature review of wound dressings and grafts.**
56.•• McPherson T, Exton LS, Biswas S, Creamer D, Dziewulski P, Newell L, et al. British Association of Dermatologists' guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in children and young people, 2018. Br J Dermatol. 2019;181(1):37–54 **British dermatologic guidelines for the management of SJS/TEN in children. Extremely detailed, step-by-step guidline for an integral treatment regimen. Provides clear recommendations for surgical vs. non-surgical approaches and suggestions for wound dressing selection.**
57.•• Creamer D, Walsh SA, Dziewulski P, Exton LS, Lee HY, Dart JK, et al. U.K. guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016. Br J Dermatol. 2016;174(6):1194–227 **British dermatologic guidelines for the management of SJS/TEN in Adults. Extremely detailed, step-by-step guidline for an integral treatment regimen. Provides clear recommendations for surgical vs. non-surgical approaches and suggestions for wound dressing selection. Also, displays a convenient treatment algorith with the diffents strengths of recommendation.**
58. Creamer D, Walsh SA, Dziewulski P, Exton LS, Lee HY, Dart JKG, et al. UK guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016. J Plast Reconstr Aesthet Surg. 2016;69(6):e119–e53.
59.• Abela C, Hartmann CE, De Leo A, de Sica Chapman A, Shah H, Jawad M, et al. Toxic epidermal necrolysis (TEN): the Chelsea and Westminster Hospital wound management algorithm. J Plast Reconstr Aesthet Surg. 2014;67(8):1026–32 **Presents the treatment experience of a burns center in the UK. Provides a pragmatic wound management algorithm, including sequential severity stages and their respective treatment recommendaiton. The role of debridement, emollients, antimicrobial dressings, and skin grafts is precisely discussed.**
60. Evans J. Topical treatment protocol for Stevens-Johnson syndrome and toxic epidermal necrolysis: a brief report. J Wound Ostomy Continence Nurs. 2009;36(5):509–11.

61. Castillo B, Vera N, Ortega-Loayza AG, Seminario-Vidal L. Wound care for Stevens-Johnson syndrome and toxic epidermal necrolysis. J Am Acad Dermatol. 2018;79(4):764–7.e1
62.• Ingen-Housz-Oro S, Duong TA, Bensaid B, Bellon N, de Prost N, Lu D, et al. Epidermal necrolysis French national diagnosis and care protocol (PNDS; protocole national de diagnostic et de soins). Orphanet J Rare Dis. 2018;13(1):56 **Guideline and recommendations from the French National Reference Center for Toxic Bullous Dermatosis for the diagnosis and management of epidemal necrolysis. Proposes a non-surgical management, recommending the non-removal of the detached epidermis.**
63. Mahar PD, Wasiak J, Hii B, Cleland H, Watters DA, Gin D, et al. A systematic review of the management and outcome of toxic epidermal necrolysis treated in burns centres. Burns. 2014;40(7):1245–54.
64. Le HG, Saeed H, Mantagos IS, Mitchell CM, Goverman J, Chodosh J. Burn unit care of Stevens Johnson syndrome/toxic epidermal necrolysis: a survey. Burns. 2016;42(4):830–5.
65. Dodiuk-Gad RP, Olteanu C, Jeschke MG, Cartotto R, Fish J, Shear NH. Treatment of toxic epidermal necrolysis in North America. J Am Acad Dermatol. 2015;73(5):876–7.e2.
66. Cartotto R. Burn Center Care of Patients with Stevens-Johnson syndrome and toxic epidermal Necrolysis. Clin Plast Surg. 2017;44(3):583–95.
67. Dreyfuss DA, Gottlieb LJ, Wilkerson DK, Parsons RW, Krizek TJ. Survival after a second episode of toxic epidermal necrolysis. Ann Plast Surg. 1988;20(2):146–7.
68. Imahara SD, Holmes JH, Heimbach DM, Engrav LE, Honari S, Klein MB, et al. SCORTEN overestimates mortality in the setting of a standardized treatment protocol. J Burn Care Res. 2006;27(3):270–5.
69.•• McCullough M, Burg M, Lin E, Peng D, Garner W. Steven Johnson Syndrome and Toxic Epidermal Necrolysis in a burn unit: a 15-year experience. Burns. 2017;43(1):200–5 **SJS/TEN management experience of an academic center in California. Provides a comprehensive treatment algorithm for SJS/TEN. Proposes debridement of devitalized epidermis and discusses the use of protective dressings and topical therapy.**
70. Lindford A, Vuola J. Re: toxic epidermal necrolysis (TEN): the Chelsea and Westminster hospital wound management algorithm. J Plast Reconstr Aesthet Surg. 2015;68(2):288–9.
71. Lindford AJ, Kaartinen IS, Virolainen S, Vuola J. Comparison of Suprathel(R) and allograft skin in the treatment of a severe case of toxic epidermal necrolysis. Burns. 2011;37(7):e67–72.
72. Kakagia DD, Karadimas EJ. The efficacy of Versajet hydrosurgery system in burn surgery. A systematic review. J Burn Care Res. 2018;39(2):188–200.
73. Ferrer-Sola M, Sureda-Vidal H, Altimiras-Roset J, Fontsere-Candell E, Gonzalez-Martinez V, Espaulella-Panicot J, et al. Hydrosurgery as a safe and efficient debridement method in a clinical wound unit. J Wound Care. 2017;26(10):593–9.
74. Legemate CM, Goei H, Gostelie OFE, Nijhuis THJ, van Baar ME, van der Vlies CH. Application of hydrosurgery for burn wound debridement: an 8-year cohort analysis. Burns. 2019;45(1):88–96.
75. Edwards K, Stokes H, Suttle K, Potts C, Coles K. Topical treatment protocol for Stevens-Johnson syndrome and toxic epidermal necrolysis. J Wound Ostomy Continence Nurs. 2009;36(3):330–4.
76. Rogers AD, Blackport E, Cartotto R. The use of Biobrane((R)) for wound coverage in Stevens-Johnson syndrome and toxic epidermal necrolysis. Burns. 2017;43(7):1464–72.
77. Asz J, Asz D, Moushey R, Seigel J, Mallory SB, Foglia RP. Treatment of toxic epidermal necrolysis in a pediatric patient with a nanocrystalline silver dressing. J Pediatr Surg. 2006;41(12):e9–12.
78. Khundkar R, Malic C, Burge T. Use of Acticoat dressings in burns: what is the evidence? Burns. 2010;36(6):751–8.
79. Palmieri TL, Greenhalgh DG, Saffle JR, Spence RJ, Peck MD, Jeng JC, et al. A multicenter review of toxic epidermal necrolysis treated in U.S. burn centers at the end of the twentieth century. J Burn Care Rehabil. 2002;23(2):87–96.
80. Tredget EE, Shankowsky HA, Groeneveld A, Burrell R. A matched-pair, randomized study evaluating the efficacy and safety of Acticoat silver-coated dressing for the treatment of burn wounds. J Burn Care Rehabil. 1998;19(6):531–7.
81. Smith SD, Dodds A, Dixit S, Cooper A. Role of nanocrystalline silver dressings in the management of toxic epidermal necrolysis (TEN) and TEN/Stevens-Johnson syndrome overlap. Australas J Dermatol. 2015;56(4):298–302.
82. Zou SB, Yoon WY, Han SK, Jeong SH, Cui ZJ, Kim WK. Cytotoxicity of silver dressings on diabetic fibroblasts. Int Wound J. 2013;10(3):306–12.
83. Choi H, Castillo B, Seminario-Vidal L. Silver absorption in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis treated with silver-impregnated dressings. A case series. Int Wound J. 2018;15(6):1049–51.
84. Varas RP, O'Keeffe T, Namias N, Pizano LR, Quintana OD, Herrero Tellachea M, et al. A prospective, randomized trial of Acticoat versus silver sulfadiazine in the treatment of partial-thickness burns: which method is less painful? J Burn Care Rehabil. 2005;26(4):344–7.
85. Yin HQ, Langford R, Burrell RE. Comparative evaluation of the antimicrobial activity of ACTICOAT antimicrobial barrier dressing. J Burn Care Rehabil. 1999;20(3):195–200.
86. Mosti G, Magliaro A, Mattaliano V, Picerni P, Angelotti N. Comparative study of two antimicrobial dressings in infected leg ulcers: a pilot study. J Wound Care. 2015;24(3):121–2 4-7.
87. Gentili V, Gianesini S, Balboni PG, Menegatti E, Rotola A, Zuolo M, et al. Panbacterial real-time PCR to evaluate bacterial burden in chronic wounds treated with Cutimed Sorbact. Eur J Clin Microbiol Infect Dis. 2012;31(7):1523–9.
88. Borkow G, Gabbay J, Dardik R, Eidelman AI, Lavie Y, Grunfeld Y, et al. Molecular mechanisms of enhanced wound healing by copper oxide-impregnated dressings. Wound Repair Regen. 2010;18(2):266–75.
89. Tenaud I, Sainte-Marie I, Jumbou O, Litoux P, Dreno B. In vitro modulation of keratinocyte wound healing integrins by zinc, copper and manganese. Br J Dermatol. 1999;140(1):26–34.
90. Kirsner RS, Amaya R, Bass K, Boyar V, Ciprandi G, Glat PM, et al. Effects of a surfactant-based gel on acute and chronic paediatric wounds: a panel discussion and case series. J Wound Care. 2019;28(6):398–408.
91. Salisbury AM, Percival SL. Efficacy of a surfactant-based wound dressing in the prevention of biofilms. Adv Skin Wound Care. 2018;31(11):514–20.
92.• Young JB, Gondek SP, Troche M, Summitt JB, Rae L, Thayer WP, et al. The use of porcine xenografts in patients with toxic epidermal necrolysis. Burns. 2016;42(8):1728–33 **Retrospective review of use of porcine xenografts in SJS/TEN patients. Presents evidence of wound pain reduction after the application of the porcine xenograft. Evaluates the utility of these advance dressings and recommend their placement in patiens with >20% of involved body surface area.**
93. Alavi A, Kirsner R. Dressings. In: Bolognia J, Schaffer JV, Cerroni L, editors. Dermatology (Basel, Switzerland). 4th ed: Elsevier Limited; 2018. p. 2462–77.
94. Heimbach DM, Engrav LH, Marvin JA, Harnar TJ, Grube BJ. Toxic epidermal necrolysis. A step forward in treatment. Jama. 1987;257(16):2171–5.
95. Birchall N, Langdon R, Cuono C, McGuire J. Toxic epidermal necrolysis: an approach to management using cryopreserved allograft skin. J Am Acad Dermatol. 1987;16(2 Pt 1):368–72.

96. Pianigiani E, Ierardi F, Taddeucci P, Perotti R, Biagioli M, Di Simplicio FC, et al. Skin allograft in the treatment of toxic epidermal necrolysis (TEN). Dermatol Surg. 2002;28(12):1173–6.
97. Bradley T, Brown RE, Kucan JO, Smoot EC 3rd, Hussmann J. Toxic epidermal necrolysis: a review and report of the successful use of Biobrane for early wound coverage. Ann Plast Surg. 1995;35(2):124–32.
98. Arevalo JM, Lorente JA. Skin coverage with Biobrane biomaterial for the treatment of patients with toxic epidermal necrolysis. J Burn Care Rehabil. 1999;20(5):406–10.
99. Bannasch H, Kontny U, Kruger M, Stark GB, Niemeyer CM, Brandis M, et al. A semisynthetic bilaminar skin substitute used to treat pediatric full-body toxic epidermal necrolysis: wraparound technique in a 17-month-old girl. Arch Dermatol. 2004;140(2):160–2.