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Review Article

Toxic epidermal necrolysis - management issues and treatment options

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Abstract: Toxic epidermal necrolysis (TEN) and Steven-Johnson syndrome (SJS) are characterized by extensive necrosis and cleavage of the epidermis from the dermis akin to a superficial or partial thickness burn. Sepsis is the usual cause of mortality but much of the pathophysiologic process results from an outpouring of cytokines and matrixmetalloproteinases (MMPs) which have a destructive effect on the extracellular matrix and may play a part in the epidermal/dermal cleavage seen with this disease. Recent attention has been focused on the modulation of proteases in an attempt to decrease the MMP-mediated destruction. Nanocrystalline silver (NCS) is one such agent that has good anti-microbial efficacy, but is also effective in modulating MMP levels. Twelve cases of confirmed TEN that were treated with NCS were analyzed with a view to assessing efficacy and setting logical guidelines for managing this condition, particularly in relation to immunosupressed patients. From this study important issues have been highlighted for discussion.

Keywords: Toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), Sepsis, matrixmetalloproteinases (MMPs), Nanocrystalline silver (NCS), treatment, burn

Introduction

Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN, Lyell's syndrome) is a serious adverse skin reaction that can be life threatening. SJS is considered a minor form of TEN characterized by less than 10% total body surface area (TBSA) of skin detachment, and an average reported mortality of 1-5%, whereas TEN is characterized by more than 30% skin detachment, and an average reported mortality 25-35% [1]. Both conditions are characterized by keratinocyte apoptosis and cleavage of the epidermis from the dermis resulting in exposure of large areas of dermis akin to superficial and partial thickness burn injuries. In this paper TEN will be used to denote both conditions.

Drugs most commonly associated with TEN are antibiotics such as sulfonamides, tetracyclines and quinolones; anticonvulsants such as phenytoin, phenobarbital and carbamazapine; antiretroviral drugs; nonsteroidal anti-inflammatory drugs; and allopurinol [1].

Most reports of TEN management concentrate on resuscitative and supportive strategies with the primary concern that of avoiding infection. Management principles commonly involve those used to treat superficial or partial thickness burns. This works well in relation to the outward manifestation of the disease but little attention has been focused on topical treatment relating to the pathophysiologic background of this disease. Although sepsis is currently accepted as the main cause of mortality, much of the morbidity and subsequent threat to life is orchestrated by an exaggerated inflammatory response with major outpouring of cytokines and destructive matrixmetalloproteinases (MMPs). These mediators and proteinases cause intense destruction of the extracellular matrix, major fluid shifts and a systemic inflammatory response (SIRS) that has life threatening consequences [2]. Nanocrystalline silver (NCS) is an agent that has proven anti-microbial efficacy, but also appears to be effective in lowering MMP levels [3,4].

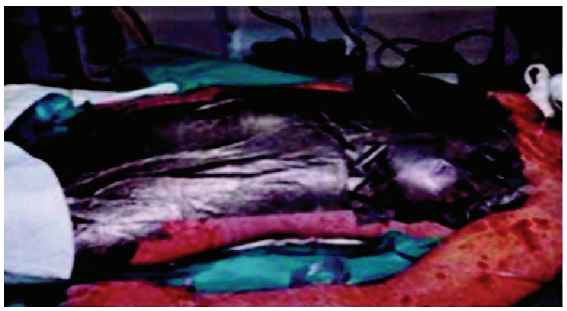

Figure 1. NCS dressings applied to TEN patient.

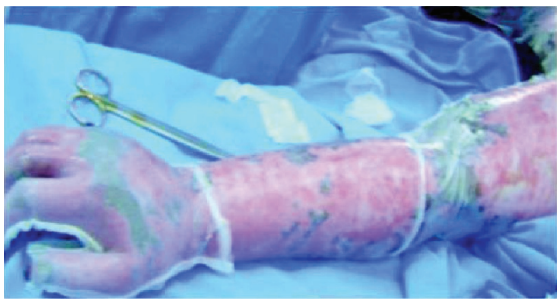

Figure 2. Biologic skin substitute (Biobrane, Smith& Nephew, Hull UK) used in areas of deeper lesions.

In the South African environment, a number of doctors use nanocrystalline silver dressings to treat patients with TEN (**Figure 1**). However, until recently, no published data existed related to the clinical outcomes and resource utilization in this patient population [5]. Twelve cases of confirmed TEN being treated with NCS were analyzed with a view to assessing efficacy of the treatment and investigating characteristics of the patient population [5]. A small study such as this has limitations in terms of absolute guidelines but the study has initiated discussion relating to some treatment are and background pathophysiologic targeting that has relevance internationally.

Background

In a recent published study 12 cases of TEN were analyzed in terms of treatment responses, background diseases and topical management issues. Eleven out of 12 cases were classified in the TEN diagnostic group; One patient (22% TBSA) was in the intermediate group between SJS and TEN (no pure SJS patients); TBSA involvement ranged from 22% -100% (mean 64%); Two patients in the series died (16.6%). All patients had a clinically confirmed diagnosis of TEN.

The dressing routine involved the following steps: 1) Wound cleansing with water, saline, or diluted chrlorhexidine and dry skin fragments being removed; 2) operating room (OR) debridement was undertaken where deemed necessary by the physician. In some cases debridement was carried out using Versajet apparatus (Smith & Nephew, Hull UK); 3) Hydrogel liquid was applied to wounds in many cases to help with activation of the NCS dressing; 4) Acticoat (Smith & Nephew Hull UK) was applied over the gel. In the majority of cases classic Acticoat (three layered dressing) was used; 5) A secondary absorbent dressing (usually foam) was applied if excess moisture/exudate was anticipated; 6) Most dressings were changed every 3 days unless excess exudate dictated daily dressings for the first few days (3/12, 25% of cases); 7) Acticoat dressings were stopped when epithelialization was judged to be 90% complete; 8) If the wound was considered to be deep partial thickness or deeper, or where scarring/contracture was considered to be a real possibility, a biologic skin substitute was introduced to the dressing regimen (**Figure 2**) (Biobrane, Smith & Nephew Hull UK).

The group was made up of 7 female patients and 5 male patients; Age varied from 8 to 52 yrs (mean 31yrs). Background diseases included diabetes, tuberculosis (TB); immunocompromized state; epilepsy; varied respiratory problems, head injuries, depression, addiction rehabilitation. The average number of days from the onset of SJS/TENS to diagnosis was 4.6 (+3.8), (median 3.0, range 1 – 10). The majority of cases involved sulfonamides (50% -6/12) or carbamezapine (33.3% -4/12) as causative agents; Epilepsy prophylaxis was involved in 42% of cases (5/12) -epilepsy was diagnosed in only one of these cases. The mean number of days of exposure to the causative agent was 5.8 days (range 1 – 24). All cases presented with superficial to partial thickness (I case 6% deep partial thickness within 22% TBSA) wounds; no full thickness wounds resulted and no skin grafting was necessary. Two deaths occurred in the series related to respiratory failure (16.6%). Intravenous steroids were used in one case and intravenous immunoglobulins in 2 cases of the 12 (16%).

The most common organisms isolated included *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Enterobacteriaceae* species with blood borne septicemic disease confirmed in only 1 case. Only two cases (both 100% exposure) had significant sepsis problems. Two cases of septicemia were seen, one of which resolved completely over a few days. Long term fever or other symptoms and signs of infection were not apparent following the application of the dressing regimen, other than in one recorded case.

Acticoat dressings were stopped when epithelialization was judged to be 90% complete. Time to healing ranged from 12 days to 65 days (mean 23 days). A biological skin substitute (Biobrane) was added to the dressing regimen in 3 of 12 cases (25%) and Versajet debridement was carried out in 3 cases (25%).

As discussed above, TEN is well described and recognized in the literature as amongst the most severe skin reactions involving widespread cleavage of the epidermis from the dermis (**Figure 3**). The spectrum of disease presented in this series is typical of other reports relating to TEN but certain issues emanating from this study warrant further discussion.

IV Treatment (corticosteroid and immunoglobulins) and debridement

Treatment with systemic steroids has been associated with an increased prevalence of complications and its use remains controversial [1]. Corticosteroid usage has been abandoned as a standard component of intravenous therapy (used in one case in this series). The ophthalmology literature contains several papers that advocate systemic and topical steroids to minimize ocular morbidity [15-19]. Treatment with steroids thus appears to be limited to that directed against ocular complications. Additionally the role of immunosuppressants in this context is not well understood and is not considered standard [1]. The role of intravenous immunoglobulins (IVIG) is worthy of further discussion.

One of the largest study involving IVIG was a multicenter study of 48 patients with TEN. Success was concluded based upon an 88% survival rate, but also the rapid (mean of 2.3 days) cessation of skin and mucosal detachment in

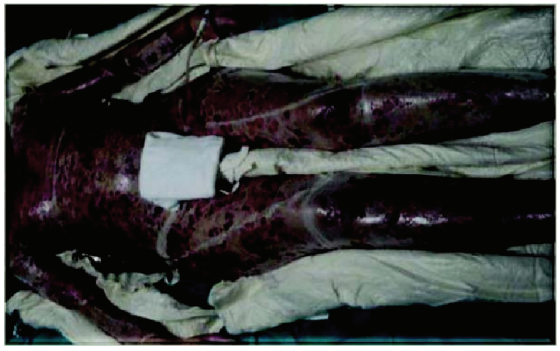

Figure 3. Typical widespread involvement of TBSA in TEN patient.

89.6% of patients. Mortality was associated with a lower dose of IVIG, longer time of onset to IVIG use, co-existing underlying chronic conditions, older age, and greater body surface area involved [9-13]. Brown et al [12] reported on 45 patients with TBSA epidermal detachment of 45%, among which 21 were treated with standard therapy while other 24 with IVIG. Mortality was 42% in the IVIG group versus 29% in the standard care group. Mortality in the IVIG treated group was also higher than that predicted by SCORTEN (38%). These surprising results were discussed by French et al [14] - several features of this study were noted as unusual. Wound debridement, a practice that is no longer routinely recommended [1], was performed on all patients at admission. The authors suggest that the association of IVIG treatment and debridement may have impacted on the poor outcome in the study. Additionally the low dose and late administration of IVIG may have contributed to the surprising results [1].

The size of this series precludes us from making any definite decisions in this regard. However some observations are appropriate – IVIG did not seem to have an impact on prognosis in these cases [5]; debridement did not seem to affect healing time or prognosis. Additionally a total of 6 blood transfusions were administered – 3 of 4 of these patients wounds were debrided, 3 of 8 were not debrided; the trend appears to demonstrate a likelihood of debridement being followed by blood replacement, although other variables may be possible. It appears that aggressive debridement should be restricted unless absolutely necessary -in most cases a controlled gentle washing/debridement should suffice.

This is further complicated in HIV positive patients. These patients are more prone to TEN when their CD4 counts are high (able to mount a response). Administration of IVIG may help to douse the immune response and theoretically halt the process of skin separation. However it is unknown whether debridement and exposure of large areas of wounds in patients who have now decreased CD4 counts, makes them more susceptible to infective complications. An alternative therapeutic agent that halts the skin separation process without systemic immune modulation would be preferable. This may be possible with the right choice of dressing, an important focus of this paper.

Background disease/immunosupression

The SCORTEN Scale is a severity-of-illness scale with which the severity of certain bullous conditions can be systematically determined. It was originally developed for Toxic Epidermal Necrolysis [7]. In the SCORTEN Scale 7 independent risk factors for high mortality are systematically scored, so as to determine the mortality rate for that particular patient.

In this series, the SCORTEN system proved to be only partially useful. Prognostic factors were significantly increased in the 2 cases that died (scored 3 and 4 respectively) but the chart did not accurately reflect the significance of the background diseases that appeared to play a dominant role in the death of these patients. Although the HIV status does not necessarily confer added risk (discussed later), it appears that HIV combined with another background illness severely compromises the prognosis. In this series the two patients that died were both HIV positive, one compounded by severe pulmonary tuberculosis, the other with advanced diabetes. Had these factors been taken into account by changing the risk parameter to associated malignancy / immunocompromized /co-existent severe chronic disease, both these cases would have been classified as '5 or more' in the prognostic scale with a >90% mortality. This is even more apparent when one considers that the patient with severe HIV and pulmonary TB was a young adult, had 35% TBSA wounds but was overwhelmed by respiratory system failure.

Causative drugs/HIV

Use of therapeutic drugs is reported in over 95% of patients with TEN. Many drugs have been identified as causative agents and the drugs in this series appear to be typical of those reported previously [1,8,21,22]. With the advent of greater numbers of HIV positive cases however, anti-retroviral drugs (ARVs) have come into focus. More particularly nevirapine has been reported as a cause of TEN in some reports [23,24]. Metry et al reported Stevens-Johnson syndrome in 2 HIV patients treated with nevirapine and mentioned one other in the literature [25]. Although sulfonamide drugs have been the most common cause of adverse skin reactions in HIV-infected patients for many years [24], nevirapine (NVP) has become the leading cause of severe skin reactions in these patients during the past decade [24]. Although the incidence of NVP-related rash is reported to be as high as 36.0%, the frequency of TEN described in HIV patients on ARVs is relative low, between 0.3–1.5% [23-27]. Risk factors for NVP-related rash include female sex, high baseline CD4 cell count, history of drug allergy, lower body weight, high NVP plasma level and probably certain human leukocyte antigen types [23-27].

Allied to this, many patients are treated for complications of HIV infection, particularly respiratory complications/pneumonia (*pneumocystis carinii -PCP*) with sulfonamide anti-biotics. This increases the risk of TEN considerably, particularly in cases with high CD4 counts. The overlap of sulfonamide and nevirapine therapy in these patients, may make identification of the causative agent more difficult. It is important that physicians are aware of the potential problems associated with these drugs in this group of patients. Sulfonamide anti-biotics appear to be particularly troublesome in this regard and it may be time to seek alternatives or to strictly control the time of exposure to these drugs (see below) when dealing with respiratory complications of HIV disease. Physicians should consider the risk of the life-threatening cutaneous reactions when prescribing a change to a NVP based regimen in patients with a high CD4 count. In this series it is important to note that the HIV status of many of the patients on sulfonamide anti-biotics was not known or disclosed. In keeping with South African laws of confidentiality, this information was not forthcoming. Thus it is possible that more of these cases were HIV positive. It is noteworthy that of the two cases that died, both were HIV positive, one with advanced HIV disease and pulmonary TB and the other with advanced diabetic disease. Thus,

again the importance of severe co-morbidities, is stressed.

The current regimen in dealing with HIV patients in many situations involves using sulfonamide antibiotics as prophylaxis against PCP when CD4 counts are low. Once ARVs are started and the CD4 counts rise to an acceptable level, the sulfonamides are stopped. Although difficult to ascertain from this study, it is likely that as CD4 counts increase patients are likely to be susceptible to TEN if they are on sulfonamide antibiotics. Thus a consideration for a treatment regimen would be a halt to sulfonamides as soon as the CD4 count starts responding and rising rather than waiting for it to reach high levels, especially if they are being used prophylactically. This is worthy of further discussion with physicians. Of course this will help if the TEN is a result of sulfonamide exposure – if Nevirapine is the cause, the problem persists. It would appear that in cases of immunosupression, patients appear to be more susceptible to TEN outbreaks as their immune status improves. It is during this transition of immunity that careful drug choices and usage or limitations should be borne in mind by managing physicians.

An additional observation in this series that warrants discussion concerns the use of anti-epileptic prophylaxis or the use of these drugs in patients without documented epilepsy. In this series only one patient was reported as having diagnosed epilepsy. The other 4 cases were prescribed anti-epileptic drugs for head injury, meningitis, depression and as part of a rehabilitative program. Circumspection is needed when choosing drugs especially when they are selected prophylactically.

It is likely that lower respiratory tract involvement was a major factor in the two deaths in this series. Both these cases died of respiratory distress and both were immunocompromized (HIV), one case being compounded by pulmonary tuberculosis (TB). TBSA in these cases was 35% and 60% and the wounds did not appear to have presented a major problem in the management of these cases.

Nanocrystalline silver (NCS)

The pathogenesis of TEN involves separation or cleavage at the dermoepidermal junction. It has been suggested that MMPs (particularly gelatinases MMP 2, 9) secreted by keratinocytes are able to degrade macromolecular components of the basement membrane. This may be one of the mechanisms of this disease process [29]. The role of MMPs has to be correlated with the main pathogenic mechanism in TEN which involve FAS-FASL keratinocyte apoptosis [28,30]. Increased gelatinase activity in the culture medium of skin from TEN and SJS patients maintained in organ culture and in blister fluid may be responsible for the detachment of the epidermis in these drug-induced necrolyses [28,29,30].

As with many other inflammatory conditions, the control of MMPs and their destructive effects appears to be critical. Recent papers have suggested that apoptosis of cells (endothelial, neural etc) in varying disease processes may be as a direct result of MMP-9 release that in turn causes a release of extracellular soluble FasL [43,44]. If this is the case the control of MMP-9 should affect the entire cleavage and apoptotic process seen in TEN.

This is where NCS has become a potential therapeutic modality for control of these conditions. Acticoat nanocrystalline silver dressings exert rapid (within 30 minutes) and potent (releasing active silver at a level of 70 – 80 ug/ml) antibacterial action that is sustained for a period of 3 days [31]. Not only does NCS have a broad, effective, well accepted potency against bacterial and fungal organisms, but the Ag^0 ion appears to offer significant protease modulating effects [3-5,32-34]. This is particularly evident against MMP-9, the destructive gelatinase responsible for much of the destruction in the wound milieu of chronic non-healing wounds, chronic wound fluid corrosive effects and in some acute (dermatitic) conditions [35-37].

MMP-9 coordinates and effects multiple events involved in the process of epithelial regeneration [35,38]. In an acute surgical wound, MMP-9 is transiently expressed [38]. In contrast MMP-9 is persistently elevated in chronic wounds. Increased MMP-9 is seen in decubitus ulcers, venous stasis ulcers and non-healed burn wounds. As these wounds heal, MMP-9 disappears [35-37].MMP-9 is not expressed in normal, uninjured skin [38]. Reis et al. [38] speculate that the excess MMP-9 found in the centre of burn wounds, or in the chronic wound milieu,

prevents reconstitution of the normal dermal and epidermal structures. According to these authors, the complicated interplay between the matrix attachment molecules, cytokines, inhibitors and activators in the wound environment becomes disjointed and unbalanced in the wound that fails to heal [38]. The TEN epidermal cleavage effect appears to fit well into this model of MMP-9 excess [3-5,35].

Most of the research that unearthed the anti-MMP-9 effect of NCS started with studies done in a contact dermatitis porcine model. Contact dermatitis is associated with potent inflammation and raised MMP-9 levels. NCS was shown to be more effective than traditional anti-inflammatory agents (silver nitrate etc) in lowering inflammatory mediators [3-5,35].The decreased inflammation in the nanocrystalline silver treated group was associated with increased inflammatory cell apoptosis, a decreased expression of proinflammatory cytokines, and decreased gelatinase (MMP-9) activity. These data offer support that a species of silver (Ag0) that is uniquely associated with nanocrystalline silver may be responsible for the protease modulating activity and improvement in healing [4]. Results suggest that at higher pHs more of the total silver in solution is actively anti-inflammatory, likely related to Ag0 clusters [4,35]. The Ag+ released into solution react with hydroxyl ions forming calcium hydroxide in solution [39] causing precipitation, resulting in a greater amount of Ag0 species being available to effect its anti-inflammatory properties.

Considering these facts related to the disease entity and the therapeutic effects of NCS, it would appear that this is an ideal agent for topical application to the acute wound of TEN. The protease modulating effects and efficacious bioburden diminishing abilities appear to halt the destructive process and decrease complications. Although this is a small series, the use of NCS appears to have been very effective in achieving these goals. This report echoes similar findings in other reported series or case reports [8,41]

Recommended treatment

From the authors perspective it is important that this study is not misconstrued as one only advising the products mentioned here. Thus many forms of foams, exudate absorbent dressings and other hydrogels may well be acceptable to use in these cases. In fact the use of Versajet for debridement, I believe is not indicated in most TEN cases. However, NCS (and to an extent, Biobrane) appear to be real advances in the management of TENS.

Based on the findings of twelve cases in this series, a provisional guideline was suggested for the management of TEN [5]. This was aimed at limiting disease progression and preventing infection: 1) An acute awareness of the condition is important so that appropriate drug choices can be made recognizing their potential for initiating this complication. Also prophylactic sulfonamide anti-biotics in HIV patients on ARVs should be stopped as soon as CD4 counts are seen to be rising; 2) Treatment as for an acute burn -admission to a burn wound centre or specialized burn section if possible; resuscitative measures; anti coagulation with low dose heparin should be considered in all cases as one would when treating comparable burn injuries; 3) Initial and continued debridement is controversial. In most cases, the nature of the pathology appears to suit a mechanical gentle wash rather than an aggressive debridement. Thus Versajet [40] is not indicated in most cases; 4) Many cases will be able to be dressed directly without debridement following a gentle cleansing in the ICU/high care environment. The NCS dressing should applied as soon as possible. Initial application of an hydrogel may facilitate the application of the Acticoat (NCS) dressing. Choices are available of Acticoat or Acticoat Flex (Smith & Nephew Hull, UK) making it easier to choose an appropriate dressing suited to the wound circumstance. Thus the amount of exudate, anatomic areas involved, and nature of the wound will determine which Acticoat dressing would be used. The ideal situation is changing the dressing every 3rd day (or longer) if possible. This has distinct advantages of encouraging healing with minimum exposure of the wounds. It is also advantageous in terms of pain control, an exceedingly important component of the healing process. A secondary absorptive dressing is applied if deemed necessary; 5) Should the wound be assessed to be deeper (deep partial thickness) or in contracture prone anatomic areas, a biologic skin substitute is an excellent addition to the process. This aids in dermal regeneration and can avoid potential scarring and contractures in anatomically prone areas [42]. Additionally, a biologic skin substi-

tute also reduces exudate loss, reduces pain and decreases the number of dressings, so it may be chosen as a primary dressing in combination with Acticoat in many cases even where depth is not in question, but where anatomic areas are prone to contractures (neck,hands, feet, elbows etc). In this series Biobrane (Smith & Nephew Hull UK) was successfully used in appropriate cases. The skin substitute is place on the wound first, followed by the NCS dressing; 6) The combination dressings are changed when they appear saturated with wound exudate or if the wound appears to have dried. The regime is continued until 90% healing is achieved. Most of these areas may then be left exposed with moisturizing agents used to prevent dessication; 7) Sytemic therapeutic interventions are applied on an individual basis according to circumstances. This includes intravenous anti-biotics, blood replacement and systemic respiratory or cardiac support agents (inotropes, volume expanders, diuretics etc). IVIG use is still undecided; 8) Enteral feeds are preferred to parenteral feeds.

Conclusion

TEN is a devastating disease with significant mortality if not diagnosed and managed early and aggressively. It is likely that with more immunocompromized patients as a result of disease or treatment modalities, increasing numbers of TEN are likely to be seen.

In keeping with newer strategies to influence systemic outcome by targeting the local wound interface, dressings are being used not only to aid in healing, but to control sepsis and to decrease the destructive inflammatory component of the disease. NCS is one such agent that has an effective anti-bacterial spectrum, but also has the potential of modulating the protease activity influencing the inflammatory component of the disease. Together with biologic skin substitutes it can serve as an effective means to promote healing, control pain and prevent contractures in a potentially devastating disease process.

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