

# SciTz

## Dermatology

RECEIVED: 18-10-2017

ACCEPTED: 10-11-2017

PUBLISHED: 15-11-2017

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### CITATION

Mwageni N, Masenga JE, Mavura D, and Naafs B. (2017). Management of TEN in developing countries: Care and Clinical skills. 2017. 2(1): 1002.

### KEYWORDS:

Toxic epidermal necrolysis; Treatment; Resource poor conditions; Child; Traditional herbal medication

## MANAGEMENT OF TEN IN DEVELOPING COUNTRIES: CARE AND CLINICAL SKILLS

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### Abstract

This is a case report of a young patient with toxic epidermal necrolysis (TEN) treated in a resource-poor country. It gives a short review of the causes leading to this condition and discusses the immunopathology and the treatment of TEN with emphasis on the problems encountered. The most plausible cause was traditional herbal medication.

### Introduction

Toxic Epidermal Necrolysis (TEN) is an acute life-threatening muco-cutaneous disease that is seen infrequently and treated in specialized centres in developed countries. The disease is the result of massive cell death at the dermal epidermal junction and above, producing large areas of epidermis detached from the dermis, resulting in "scalded skin". Extensive mucous membrane involvement, high fever and severe "skin" pain are typical [1,2]. The patient can hardly be touched, a slight peri-lesional tangential pressure applied by the examiner's finger will immediately detach the epidermis from the dermis. The patient is usually extremely anxious. The denuded skin may give rise to extensive electrolyte, albumin and water loss [1,2]. The disease is generally precipitated by drugs or their metabolites [1,2].

The disease (TEN) is not that uncommon in developing countries. It generally occurs in HIV patients because of the used drugs such as Nevirapine and sulpha-containing drugs (cotrimoxazole). Fansidar, another sulpha-containing drug, used as anti-malarial is another culprit. The cheap and thus often used anti-epileptic drugs such as barbiturates and Phenytoin contribute to the problem. Some anti-Tb drugs such as Thioacetazone and the anti-gout drug Allopurinol add to the risk for TEN. The extensive use of indigenous herbal medicines in developing countries may also contribute [3]. Combinations of these drugs with the anti-gout drug Allopurinol may increase the risk many times and in HIV even up to a thousand fold [1]. TEN may start any time between 1-3 weeks, even earlier if the drug has a previous history

of luxating an adverse reaction [4]. Sometimes, there may be a delay of up to 2 months [1].

Treatment is extremely difficult. It includes immediate stopping of the offending drug, starting supportive therapy and considering adjunctive therapies. Supportive therapy targets the manifestations and complications of acute skin failure and includes monitoring of the fluid-electrolyte balance and providing enteral or parenteral nutrition, wound care and treatment of sepsis [5]. This must be done with drugs not suspected to induce TEN. In addition, care of the affected mucosal surfaces is required via the use of aggressive ocular lubrication, topical corticosteroids, hygienic mouthwashes and oral anaesthetics, together with monitoring temperature, blood pressure, blood sugar, urinary output and turbidity.

The following case report illustrates the difficulties that are encountered in the management of TEN under resource constraint conditions.

## Case Report

An 11-year-old Maasai boy was brought by his father to our hospital with a two weeks history of an initial pruritic erythematous rash over the trunk, the upper and the lower limbs. He later had erosions in and around the mouth and the genitalia and on the arms and the legs. The itchy rash was according to the father associated with the consumption of local fruits when he cared for the grazing cattle. When he came home with the cattle, the boy was initially given traditional herbal medication, which did not improve his condition, but instead he developed "erosions" on the legs in and around the mouth and on the genitalia. His father reported no previous allopathic medication.

He was then brought to a Regional Hospital where he stayed for three days receiving 100 mg hydrocortisone 6 hourly intravenous (iv) for 3 days. He also received intravenous ceftriaxone 1g twice daily and metronidazole 500mg three times daily. However, his condition continued to worsen and he was sent to our Consultant referral hospital.

Upon arrival the patient was very ill with a temperature of 40°C and a pulse rate of 140 per minute. He had denuded areas with extensive crusts involving the face, the mouth, the neck, a part of the trunk, the genitals and the extremities. The skin involvement was over 30 % and Nikolsky's sign was positive and the skin was extremely painful. He was immediately referred to the medical intensive care unit.

The laboratory results showed that he had low haemoglobin of 9.4 g/l with a leucocytosis of  $11.17 \times 10^9/l$ , predominant neutrophils  $9.05 \times 10^9/l$ . Liver and kidney function tests were within normal limits. Electrolytes and albumin concentrations were not available.

He was started with IV ceftriaxone 1g daily and metronidazole 500 mg tds for 7 days. Intravenous administration of normal Ringers lactate was started. The mouth and the eyes were carefully washed with normal saline and ophthalmic care was instituted, the eyes were mildly involved. The severe pain he experienced was relieved with morphine administered every 6 hours. Communication barriers and lack of enough staff necessitated the father to stay with the patient. It was later discovered that the father regularly applied traditional oil and that the patient was often found under very poor hygienic conditions. The father was explained with some difficulties to stop using the oil, which however seemed not to have done any harm. The urine of the boy looked turbid. His temperature remained high despite wound care and improvement of the TEN. His blood culture revealed *Proteus vulgaris*, which was only sensitive to Meropenem, which was immediately started at 250mg tds. However, despite this drug, he kept spiking fevers. At a certain moment there was no more money for the medicines, but fortunately the boy was lucky to get donor support. He stayed at Medical intensive care unit for 22 days and at the general Dermatological ward thereafter.

However, the wound care was very difficult because the patient was frightened and because of the severe pain. The obstinate boy was reminded by his father and another Maasai that he had to become a warrior and should not cry out and could trust the helpers. This had success. He



**Figure 1:** Boy after 4 months.

had debridement of his right posterior elbow and his right buttock, which had deep decubitus wounds.

His haemoglobin was found to have dropped to 4.6 g/l. The medical students kindly donated two units of blood for him. Iron and Folic acid were also supplied. He received blood and milk mixture (Maasai food) when available. Four weeks after sloughectomy, he received split skin grafts. He continued with physiotherapy, which had started at admission, but not too fanatic at the start from his point of view due to the sensitive skin. As consequence, he developed muscle weakness; a Voluntary Muscle Test of the dorsal flexion of his right foot of 1 and his knee flexors of 4 and hip extensors of 3. Over the months of admission this improved gradually. He was discharged from hospital in good condition. He had stayed in hospital for 5 months.

## Discussion

This patient survived only thanks to financial donations from concerned people, both the locals, students (contributed also blood) and staff as well as the foreign visitors at the department. His father sold one of his few

cows. As in any of the developing countries laboratory test were either not available or sometimes too expensive or not reliable. Drugs were regularly not available. Antibiotic resistance was frequently encountered like that in most African countries [6-8]. Clinical experience was called for, all senses had to be used: vision, feeling and smell. It is remarkable how one can compensate when tests are not available.

What mattered foremost was care. Thanks to this, the boy survived as did many others before and after him. The use of local fruits as the cause of the TEN was found unlikely, till to date we have not seen it. However traditional herbal medicine used by this local tribe often gives severe reactions including TEN. (own observation) Therefore the cause of his TEN was most likely the use of this traditional herbal medication keeping in mind the fruits. Illiteracy and financial vulnerability are the major factors in driving patients towards the use of traditional medications, which are often prepared and preserved incorrectly [3].

The mechanism of TEN has still to be unravelled. The toxic theory was quickly discarded. During active TEN, on the one hand, there is a paucity of inflammatory cells at the dermis, but on the other hand there is extensive apoptosis and consequent necrosis, indicating that the immune system is involved one way or another. There appears to be a cell-mediated cytotoxic reaction against keratinocytes that leads to keratinocyte apoptosis [9,10]. Drug-specific cytotoxic T cells and NK cells may not be the sole effect or mechanism of the keratinocyte death and their action may be amplified by the production of multiple cell-death mediators, altered anti-apoptotic pathways and altered or defective regulation of drug-specific immune reactions [2]. Various cytotoxic proteins and cytokines have been implicated as mediators of apoptosis in TEN. These include granulysin, Fas-Fas ligand interaction, tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), TNF-related apoptosis-inducing ligand (TRAIL) and perforin-granzyme B [2]. Chung et al. [11], identified granulysin as the main cell death mediator involved in TEN.

The role of corticosteroids is currently under revision [5].

Some studies reported a lack of efficacy or increased mortality in their use, but the use of high doses early in the course of the disease may actually reduce morbidity and mortality [12,13]. There is no generally accepted steroid treatment for TEN [14]. However, it was reported in children that a high initial dose of steroids could be beneficial [15]. Thereafter, steroids only hinder the recovery. The benefit of initial steroids in adults is still not proved [5,14]. However, there are strong indications that they also may be beneficial [12,13].

Intravenous immunoglobulin was previously an accepted therapeutic agent in TEN. However, its efficacy is becoming more questionable. The current European guidelines on the use of intravenous immunoglobulin in dermatology indicated that it should be used early in the disease process in the absence of an alternative evidence-based therapeutic agent [16], given that the potential benefits of high-dose intravenous immunoglobulin outweighs the risks of the medication considering the disease's natural course.

Cyclosporine appears to be an effective agent as well [17], although randomised control studies are required to demonstrate its benefit and to establish the dose, the duration of therapy and the safety profile. The role of plasmapheresis, anti-tumour necrosis factor (TNF) biologics and N-acetylcysteine is promising, but further studies are required to elucidate their benefit [2]. Preventative strategies such as pharmacogenetic screening needs to be considered earnestly, with the provision of cost-effective assays with a rapid turn-around time. However, these methods in our setting are beyond reach.

## Our Usual Practice

We use intravenous dexamethasone 100mg (1.5 mg/kg) for 3 days, delivered in 60-90 minutes, and stopping thereafter. Dexamethasone is 25 times stronger than hydrocortisone. That means 600mg hydrocortisone 6 hourly for three days or 8-10 mg/kg. All this is debatable. However, the initiating drug must be stopped.

The management of skin failure is most important; the hydration, electrolytes, protein and temperature loss. Superinfections, cave: bacterial resistance.

The mucous membranes must be cared for: the eyes, the mouth, the trachea, the bronchi and the genitals.

Beside dehydration and electrolyte loss, pneumonia and sepsis are the most life-threatening.

To prevent superinfection, intravenous antibiotics are given at the start. Antibiotics which are known to cause TEN must be avoided. Medications that have traditionally been known to lead to Stevens Johnson syndrome (SJS), erythema multiforme and toxic epidermal necrolysis include sulphonamide antibiotics, penicillin antibiotics, cefixime (antibiotic), barbiturates (sedatives), lamotrigine, phenytoin (e.g. Dilantin) (anticonvulsants), trimethoprim and Fansidar. The combination of lamotrigine with sodium valproate increases the risk of SJS.

As antibiotics we use drugs like macrolides. Wound care; avoid excessive touching. Clean with potassium permanganate solution. Dress with Vaseline gauze or better silver dressings if available. We used honey for some time with reasonable results.

Keep air around the patient, let him or her be touched as little as possible, but prevent under cooling. Start with active movements as soon as possible when the risk of new lesions diminishes. Prevent urine infections and protect against insects.

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