Toxic epidermal necrolysis (TEN) : a clinical review

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Toxic Epidermal Necrolysis (TEN):

A Clinical Review

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The University of Toledo

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Dedication

I would like to take this time to dedicate this project to those who continually support me and stand behind me through the good, the bad and the ugly. To those that continually and persistently stood by my side through the darkest days of my life, I say thank you. To those that played adversarial roles, I thank you too. Without your drive to see me fail I wouldn’t appreciate the rise back to the top as much as I do. To my friends, my family, colleagues and to those that were ever told they couldn’t achieve something in life; this is dedicated to you.
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I am deeply grateful for being able share this time with such a remarkable clinician and overall great person – my advisor, Samih Bittar, M.D. Dr. Bittar not only gave his time to clinically instruct me as my preceptor, but also served as my mentor and advisor. I am forever indebted to his generosity and godly display of selflessness. The countless days of making himself available meant a lot to me and helped me accomplish my dream. He is truly the epitome of the word ‘mentor’. 

I would also like to take this time to acknowledge a very special individual that stands monumental with demonstrations full of kindness and compassion. I speak of none other than Patricia Metting, PhD. I am reminded of Dr. Metting’s guidance and willingness to tirelessly see me to the end of this journey here at the University of Toledo. I would like to thank Dr. Metting for all that she has done to aid me with all of the resources I needed along the way. I am deeply moved by your selflessness and commitment to students’ academic success.
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Introduction

Background

Toxic epidermal necrolysis (TEN), or Lyell’s syndrome, is a rare, life-threatening drug reaction characterized by the abrupt onset of widespread skin necrosis with extensive epidermal exfoliation and frequent mucous membrane involvement (Avakian, Flowers, Arujo & Ramos-Caro, 1991; Egan, Grant, Morris, Saffle, Zone, 1999; Firoz, Henning, Zarzabal & Pollock, 2012; Lissia, Mulas, Bulla & Rubino, 2009). This drug-induced reaction remains one of the most dramatic dermatologic emergencies (Revuz, 2008).

Scottish dermatologist, Alan Lyell, first used the word ‘necrolysis’ in 1956 to describe four clinical cases involving pathological necrosis of the epidermis and widespread epidermolysis. Lyell named this syndrome toxic epidermal necrosis (TEN) to “indicate a rare life threatening mucocutaneous disorder characterized by extensive and rapidly evolving, epidermal detachment, erythema and necrosis” (Lissia, Mulas, Bulla & Rubino, 2009). In Lyell’s report, he noted that the initial febrile reaction advanced to a clinical presentation that he referred to as a “scalding eruption of the skin” (Lyell, 1956). The brief high-temperature fever and scalded appearance of the skin preceded the onset of the epidermal necrolysis which exhibited large sheets of skin peeling off, leaving a raw, denuded base (Becker, 1998; Lyell, 1956). Given the clinical course of this disease, Lyell named this syndrome toxic epidermal necrolysis (TEN) and proposed that its etiological source was some circulating bacterial toxin that led to the epidermal destruction (Lyell, 1956).

Prior to the appearance of TEN in 1956, two American physicians, Stevens and Johnson discovered the pathologic process in 1922 that identified two cases of “eruptive fever associated with stomatitis, ophthalmia and disseminated ‘purplish cutaneous macules and necrotic centres’”,


which is known today as Stevens-Johnson syndrome (SJS) (Lissia, Mulas, Bulla & Rubino, 2009). It was thought at one point in time, both TEN and SJS, the pathological processes common to both diseases were previously considered to be a part of erythema multiforme (EM) (Lissia, Mulas, Bulla & Rubino, 2009). Some early reports even suggest that EM and the SJS are variants of one another with varying severities and suggest the same for TEN due to the similarities that exist amongst all three – EM, SJS and TEN. According to Letko et al. (2005), “some investigators propose that SJS and TEN are the same disease but of different severities”. This notion continues to be highly debated and there is no agreement amongst the literature concerning this notion (Lissia, Mulas, Bulla & Rubino, 2009).
**Classification**

TEN is difficult to study and define because of its relation to other skin diseases, namely Erythema multiforme (EM) and Steven-Johnson syndrome (SJS) (Becker, 1998). SJS lies at one end of the spectrum while TEN lies at the other. Although there remains no agreement surrounding a theme for these skin diseases, there has been a consensus derived within the literature that provides clinical criteria for the definitions of SJS and TEN. SJS is quantitatively defined in cases as less than 10 percent total body surface area (TBSA) involvement while TEN is quantitatively defined with a TBSA of greater than 30 percent (Lissia, Mulas, Bulla & Rubino, 2009). The cases that fall in between 10 and 30 percent TBSA are labeled “SJS-TEN overlap”.

Other criteria have been set by other authors to include clinical features and the differences between SJS and TEN. Chan et al. in 1990 recommended SJS is defined by five parameters: 1) involvement of at least two mucous membranes; 2) the presence of target lesions; 3) fever; 4) skin biopsy compatible with erythema multiforme; and 5) skin loss <20 percent total body surface area (TBSA). TEN was then defined based on the following parameters: 1) involvement of at least two mucous membranes; 2) loss of confluent sheets of epidermis leaving an exposed dermis; 3) fever; 4) erosions of at least 20 percent of TBSA; and 5) skin biopsy compatible with TEN (Chan et al., 1990).

The most widely accepted classification was formulated by Bastuji-Garin et al., (2000) and divides the spectrum into five categories:

1) **Bullous erythema multiforme (EM)**: epidermal detachment involving <10% of the body surface, coupled with localized typical targets or raised atypical targets.

2) **SJS**: epidermal detachment of <10% of the body surface in association with widespread erthematous or purpuric macules or flat atypical targets.
3) SJS/TEN overlap: epidermal detachment of 10% to 30% of the body surface coupled with widespread purpuric macules or flat atypical targets

4) TEN with spots: epidermal detachment of >30% of the body surface coupled with widespread purpuric macules or flat atypical targets

5) TEN without spots: large sheets of epidermal detachment involving >10% of the body surface without purpuric macules or target lesions.
Epidemiology

Worldwide the incidence rate associated with TEN is low, estimated in 2005 between 0.4 and 1.2 or 1.3 per million persons annually (Table 1), a very high mortality rate between 25% and 50% is associated with these episodes (Firoz, Henning, Zarzabal & Pollock, 2012; Letko et al., 2005; Lissia, Figus & Rubino, 2004; Roujeau et al., 1990). An epidemiologic study of TEN in France gave a similar incidence of 1 to 1.3 cases per million per year (Roujeau et al., 1990). However, as the years advance, the numbers of incidence seem to be escalating in other parts of the world. In May of 2012, Lee et al. reported an incidence of 1.5-2 cases per million. Worldwide, TEN has been observed in all human races (Letko et al., 2005) and in all age groups – even children, infants and newborns (Roujeau, Chosidow, Saiag & Guillaume, 1990). However, literature shows a correlation between the incidence and increasing age. The incidence increases sharply with increasing age, as does the use of drugs with aging (Roujeau, Chosidow, Saiag & Guillaume, 1990). Females are most commonly affected represented by a female-male ratio of 3:2 to 2:1. The mean age of patients is reported between the ages of 46 and 63 while the proportion of females is estimated between 61.3% and 64.3%, respectively (Letko et al., 2005). It is theorized that females have a higher incidence due to an increased drug intake compared to males (Roujeau, Chosidow, Saiag & Guillaume, 1990). Reports have also been linked to patients with HIV-1 infection, systemic lupus erythematosus, and bone marrow-transplant recipients (Becker, 1998).
Etiology

Although the etiology remains unknown in some patients, it is generally accepted that its origin is usually an idiosyncratic drug reaction (Table 2) (Letko et al., 2005). In adults, medications are responsible for up to 80 percent of the cases associated with TEN (Roujeau, Chosidow, Saiag & Guillaume, 1990). Over 220 medications have been implicated, while very few are commonly indicated as a source. The drugs most commonly involved are:

1. Antibiotics – sulfonamides (especially trimethoprim/sulfamethoxazole), β-lactam, tetracyclines and quinolones (especially ciprofloxacin);
2. Anticonvulsants – phenytoin, phenobarbital and carbamazapine;
3. Nevirapine;
4. Abacavir;
5. Nonsteroidal anti-inflammatory drugs (especially oxicams);
6. Allopurinol;
7. Lamotrigine.

A genetic predisposition appears to be correlated to the development of TEN. There is a strong association between allopurinol and carbamezapine induced TEN with HLA-B*5801 and HLA-B*1502 in the Han Chinese population from Taiwan or other Asian countries (Lissia, Mulas, Bulla & Rubino, 2009).

The EuroSCAR study conducted an evaluation to estimate the risk associated with the different drugs suspected of adverse reactions. This study analyzed patients from six European countries that were hospitalized with a diagnosis of TEN or SJS. The study confirmed the risk related to anti-infective sulfonamides, allopurinol, carbamazapine, phenobarbital, phenytoin, and oxicam nonsteroidal anti-inflammatory drugs. Strong associations were found among newer
drugs like nevirapine and lamotrigine (Lissia, Mulas, Bulla & Rubino, 2009). Other drugs such as sertraline, pantoprazole, and tramadol and were studied and found to have overall weaker associations. The EuroSCAR study concluded that most cases are still associated with the use of the older drugs.

Literature cites additional implications of TEN to include graft versus host disease (in allogenic bone marrow transplantation) (Takeda, Mitasuhashi, Kondo, Kato & Tajima, 1997) as well as different suspected etiologies that are rare exceptions that include:

(1) Exposure to industrial chemicals and fumigants

(2) Vaccine administrations

   a. Measles

   b. Diphtheria-pertussis-tetanus

   c. Poliomyelitis

   d. influenza

   e. BCG vaccine for tuberculosis

   f. Live, attenuated, morbilli-parotitis-rubella triple vaccine
Pathophysiology

Although the exact pathophysiology remains uncertain, it is widely accepted that the epidermal necrosis that occurs as a part of the TEN disease process is believed to be due to massive keratinocyte apoptosis (Firoz, Henning, Zarzabal & Pollock, 2012). Whereas cell death by necrosis is a “disorganized, nonspecific process, apoptosis is a programmed cell death that results from one of many possible mechanisms” (Khalili & Bahna, 2006). When other cell surface death receptors undergo ligation (including tumor necrosis factor (TNF), Fas, and TNF-related apoptosis-inducing ligand) they can activate the caspase system, which subsequently results in the disassembly of DNA and cell death (Khalili & Bahna, 2006). There are also death receptor-independent mechanisms that involve the release of perforin and granzyme B from cytotoxic T cells, which cause apoptosis via a caspase-dependent or caspase-independent mechanism. Apoptosis is largely mediated by the Fas-FasL interaction (Letko et al., 2005).

All cells, including keratinocytes, express a protein on their cell surface known as Fas. However, its ligand (FasL) is primarily expressed on T and natural killer cells. In order for Fas-FasL to “play an active role, lytically active FasL must be expressed at the site of epidermal cell death” (Khalili & Bahna, 2006). A study in 1998, Viard et al confirmed the widely accepted Fas-FasL interaction concept on the cell surface and further revealed that keratinocytes from TEN patients induce apoptosis in Fas sensitive (Jurkat) cells (Viard et al., 1998). Through this model, high levels of soluble FasL (sFasL) protein in “blister fluid and blood due to the cleavage and membrane-bound FasL by metalloproteases could also be explained” (Lissia, Mulas, Bulla & Rubino, 2009).

T cell cytotoxicity is mediated by the perforine-granzyme pathway. “Granule exocytosis releases granzyme and perforin from CTL membranes into the space between the CTL and the
target cell” (Lissia, Mulas, Bulla & Rubino, 2009). Perforin monomers proceed to attack the target cell membrane forming pores. Granzyme B then enters the cell either via perforin-generated pores or by binding to mannose-6-phosphate pores that become endocytosed. Granzyme B cleaves procaspase 8 which in turn activates the caspase cascade thus resulting in cell death (Figure 4).

Cytokines have recently begun to receive more attention for its role in the pathogenesis of TEN. Proinflammatory cytokines IL-1β, TNF-α, INF-γ, and IL-15 stimulate keratinocytes which lead to the increase of their intracellular as well as cell surface-bound FasL expression. INF-γ mediated FasL activation is drastically reduced by IL-10 and TGF-β1. Activation of INF-γ stimulated keratinocytes leads to subsequent and increased apoptosis (Lissia, Mulas, Bulla & Rubino, 2009). TNF-α plays a significant role as a major cytokine involved with TEN (Lissia, Mulas, Bulla & Rubino, 2009).
Clinical Presentation & Complications

The clinical course of TEN is generally divided into three phases: the prodrome phase, the acute phase and the recovery phase (Avakian, Flowers, Arujo & Ramos-Caro, 1991). TEN typically precedes its onset by a prodrome phase of symptoms that lasts 48-72 hours that includes an abrupt fever, lethargy and malaise, sore throat, cough, vomiting, diarrhea, myalgia, rhinitis, and anorexia, often times simulating an upper respiratory tract infection (Avakian, Flowers, Arujo & Ramos-Caro, 1991). The prodrome phase advances as a result of systemic toxicity and progresses into the acute phase. The acute phase of TEN presents with a persistent fever and presents changes hematologically with hypo-albuminemia, granulocytic leucopenia, anemia and also disseminated intravascular coagulation (DIC) (Lissia, Figus & Rubino, 2004). The acute phase of TEN lasts between 8 to 12 days with an ensuing fever from the prodrome phase, mucous membrane involvement, and epidermal sloughing. Mucous membrane involvement usually precedes epidermal necrolysis with mucosal erosions and denudations of the conjunctiva, buccal, trachea, bronchi, pharynx, esophagus, nasal, anus, vagina, or perineum (Avakian, Flowers, Arujo & Ramos-Caro, 1991). 30% of cases involve the respiratory tract with sloughing of the bronchial epithelium and hypoxemia (Lissia, Mulas, Bulla & Rubino, 2009). Two-thirds of patients exhibit urethritis and episodes of urinary retention (Avakian, Flowers, Arujo & Ramos-Caro, 1991). Pruritis is also observed in 32 percent of these patients (Becker, 1998). Pain generally accompanies the mucositis and stomatitis which usually reduces that patient’s ability to maintain adequate oral intake, hydration and nutrition (Avakian, Flowers, Arujo & Ramos-Caro, 1991). Usually these patients are at a high risk for dehydration and malnutrition.

Cutaneous findings of TEN are dramatic with a sudden onset of acute macular erythematous rash with bullae. This rash is typically distributed with a shape of “scattered 2-ring
target-like lesions with a dark red centre and lighter red halo, red macules with central blistering” (Lissia, Mulas, Bulla & Rubino, 2009). Skin lesions on the epidermis may begin in sun-exposed areas and often begin symmetrically on the trunk, proximal upper extremities and the face with extension upward to involve the neck. The legs and distal portions of the arms tend to be spared, not including the palms and soles (Lissia, Mulas, Bulla & Rubino, 2009). Nikolsky’s sign (epidermal separation induced by gentle lateral pressure on the skin surface) is exhibited prior to large sheets of the epidermis separating from the dermis with extensive shedding to follow. It is not uncommon for a total epidermal loss to occur within 24 hours (Lissia, Mulas, Bulla & Rubino, 2009). Due to the extensive sloughing of the epidermis, the underlying layers of the skin become vulnerable to infection (Figure 2). Septicemia is the most common cause of death due to systemic infection by the organisms, staphylococcus aureus or pseudomonas (Lissia, Mulas, Bulla & Rubino, 2009). The final phase, the recovery phase, is a period that requires another week or two during reepithelialization of the skin and mucous membranes. An average cutaneous involvement for TEN is estimated to involve 88% of the TBSA (total body surface area) while the mean duration is approximately 20 days (not including the time for recuperation) (Avakian, Flowers, Arujo & Ramos-Caro, 1991). Patients during this phase heal more rapidly than burn victims and in this phase necrolysis rarely reoccurs in areas that have began the healing process (Avakian, Flowers, Arujo & Ramos-Caro, 1991). Areas that are void of infection and not subject to physical pressure and trauma heal faster. Regeneration of new epidermal skin occurs fastest with the anterior thorax while healing is slower with the back and in intertriginous regions such as the axillae, groin, perineum and buttock (Avakian, Flowers, Arujo & Ramos-Caro, 1991). Cutaneous lesions can take up to 2 weeks to re-epithelialize and heal completely while lesions associated with the mucosa may take longer (Avakian, Flowers, Arujo & Ramos-Caro, 1991).
Diagnosis

Initially, TEN is a clinical diagnosis histologically confirmed by skin biopsy (Lissia, Mulas, Bulla & Rubino, 2009). Early stage biopsy demonstrates apoptotic keratinocytes throughout the epidermis. Histologically, a late biopsy reveals full-thickness epidermal necrosis and detachment, basement membrane vacuolar changes, subepidermal blistering, and necrotic keratinocytes in the epidermal tissue (Avakian, Flowers, Arujo & Ramos-Caro, 1991) (Figure 3). In evaluating the patient, the clinician should be aware of the non-visual signs that accompany the characteristic features of TEN. Mucosal involvement includes painful swallowing, painful urination and diarrhea (due to the gastrointestinal sloughing of the mucosa) (Avakian, Flowers, Arujo & Ramos-Caro, 1991). More than 90 percent of TEN patients develop oral lesions or ulcerations (Avakian, Flowers, Arujo & Ramos-Caro, 1991). Other non-visual signs are found with the prodrome and include fever, malaise, lethargy and myalgia (Avakian, Flowers, Arujo & Ramos-Caro, 1991). Visually, a generalized erythema with possible bullae (blisters) or target lesions and extensive, full-thickness epidermal detachment that reveals a denuded dermis is appreciated. In involved areas, Nikolsky’s sign can be visualized. Other diagnoses such as erythema multiforme (EM), impetigo, lupus erythematosus, linear IgA dermatosis, staphylococcal scalded skin syndrome (SSSS), pemphigus vulgaris, bullous pemphigoid, graft versus host disease and thermal or chemical burns should be ruled out and considered as part of the differential diagnosis (Table 3) (Lissia, Mulas, Bulla & Rubino, 2009).
Treatment

General Management

Medical management of TEN requires early diagnosis and immediate withdrawal of the offending drug, supportive therapy and specific treatment (Downey, Jackson, Harun & Cooper, 2011; Lissia, Mulas, Bulla & Rubino, 2009; Pereira, Mudgil & Rosmarin, 2007). Prompt withdrawal of the drug reduces the apoptotic stimuli. The faster the offending drug is eliminated, the better the prognosis (Pereira, Mudgil & Rosmarin, 2007). Due to the extensive skin detachment and mucosal involvement associated with TEN patients are better suited for medical management at burn units (Avakian, Flowers, Arujo & Ramos-Caro, 1991; Lissia, Mulas, Bulla & Rubino, 2009). Several sources identify the burn unit as a more suitable place (over than the wards and intensive care units) due to increased access to isolated environments, availability of appropriate wound management, constant nurse control and the availability of technologically advanced devices, such as fluidized beds (Lissia, Mulas, Bulla & Rubino, 2009). Among other benefits, authors have cited increased access to other amenities that are pertinent for pulmonary and eye care, infection, ambient temperature and stress-ulcer control, nutritional support and physical therapy (Avakian, Flowers, Arujo & Ramos-Caro, 1991). TEN requires immediate nutritional correction to aid in the healing process. According to the several experiments, enteral feeding creates optimal conditions for increased survival and has shown to be advantageous in the treatment of large wounds (Downey, Jackson, Harun & Cooper, 2011). While the preferred method of feeding is enteral feeding, it is well documented that oropharyngeal ulceration and pain makes eating, drinking and enteral tube placement difficult. In 20 percent of the cases in a particular study, nutrient absorption proved to be altered by gastrointestinal mucosa involvement (Lissia, Figus & Rubino, 2004). Therefore, it is ideal that total parenteral nutrition (TPN) be
started promptly with when no other option remains available for feeding (Downey, Jackson, Harun & Cooper, 2011; Lissia, Mulas, Bulla & Rubino, 2009).

Following the discontinuation of the offending drug, first line management is fluid and electrolyte replacement, acid-base and metabolic equilibrium regulation, serum protein and blood glucose and topical skin management. Most authors agree intravenous fluids should be administered using crytalloids with the Parkland formula in adjunct with lactated Ringer’s solution (Lissia, Figus & Rubino, 2004).

Maintenance of pain analgescics, prophylaxis for deep vein thrombosis and erosive gastric ulcers, prevention of pressure sores and infections should be addressed just as in any case with a critically ill patient (Lissia, Figus & Rubino, 2004). It is recommended that patients undergo daily physical therapy to keep the extremities mobile to prevent impaired functionality (Lissia, Figus & Rubino, 2004). Antibiotic administration and therapy should only ensue following a positive culture and antibiogram (Lissia, Figus & Rubino, 2004). There is no current literature to support any benefits of antibiotic prophylaxis however there is evidence that mortality rates range from 0 to 44 percent with specific treatment (Lissia, Figus & Rubino, 2004).

**Wound care**

There are several components necessary in the maintenance and management of the extensive skin wounds associated with TEN. In order to provide adequate wound care management, the wound dressings must: protect the wound, maintain physiologic environmental conditions for re-epithelialization and allow unrestricted movements, water vapor permeable to prevent maceration, nontoxic, nonadherent, comfortable, easy to apply, and have an acceptable price (Lissia, Figus & Rubino, 2004).
Topically, silver sulfadiazine cream is the most commonly used agent to avoid infection. However, only patients who have never exhibited a hypersensitivity to sulfonamides can use this cream (Lissia, Figus & Rubino, 2004). It can also lead to less desirable outcome that may cause further skin loss due to the frequent painful dressing changes that are needed (Lissia, Figus & Rubino, 2004). In a case study, a patient with TEN that had 90 percent total body surface area involvement was successfully treated using nanocrystalline silver dressing (Acticoat™) (Lissia, Figus & Rubino, 2004). In a recent study, another successful experience was reported with the use of AQUACEL Ag™ (composed of hydrofiber with 1.2% (w/w) silver) for a TEN patient that had 86 percent skin detachment. These options hail the benefits of being cost effective, reducing wound infection and decreasing associated pain (Lissia, Figus & Rubino, 2004).

**Pharmacological therapy**

Literature cites a number of interventions that have been tried in an effort to stop the TEN disease progression. Among those listed as treatments include systemic corticosteroids, immunosuppressants (cyclophosphamide and cyclosporin), tumor necrosis factor-alpha inhibitor agents, plamapharesis and intravenous immunoglobulin (IVIG). According to one prospective EuroSCAR Study in 2008, findings revealed that there was no evidence that any of the specific treatments were of any significant benefit. Others authors argue that there is some benefit associated with some of the treatments but overall there is no consensus that identifies one treatment to be the cornerstone of pharmacological management for TEN.

*Cyclophosphamide and cyclosporin*
Despite some of the reports that cite cyclophosphamide as valuable, it is not a medication used in the treatment of TEN (Heng, 1991). “Cyclophosphamide is a precursor of an alkylating nitrogen mustard, an antineoplastic and immunosuppressive agent that must be activated in the liver to form the active aldophosphamide” (Lissia, Mulas, Bulla & Rubino, 2009). Cyclophosphamide has historically been used in the treatment for leukemia and lymphoma and can cause significant side effects. These side effects include sterility, birth defects, genetic mutations, and cancer. Apoptosis of immunocytes occurs in a non-specific way producing its antineoplastic and immunosuppressive properties.

Cyclosporin is a “cyclic undecapeptide from an extract of soil fungi, species Beauveria nivea. It is a powerful immunosuppressant with a specific action on T-lymphocytes” (Lissia, Mulas, Bulla & Rubino, 2009). Historically, it has been used as a prophylactic agent in preventing graft rejection of organ and tissue transplants. Cyclosporin accomplishes this by blocking the T-cells from being activated and subsequently halts proliferation while the apoptotic reaction sequence is inhibited promoting the downregulation of NF-κB. Just like cyclophosphamide, their utility in the role of TEN is not well defined and therefore not part of the standard treatment of TEN.

**Systemic Corticosteroids**

Historically, corticosteroids were considered the first-line drug of choice in the treatment of TEN (Downey, Jackson, Harun & Cooper, 2011). However, while some authors report positive results (Pereira, Mudgil & Rosmarin, 2007), others report worsening effects that include increased mortality, higher rates of infection and sepsis, and increased length of stay in the hospital (Downey, Jackson, Harun & Cooper, 2011). Some authors suggest that the negative
appraisal may have been the result of inadequate dosing (Pereira, Mudgil & Rosmarin, 2007). Recently, interest has peaked in brief high dose steroid therapy within the first 48 hours (before epidermal sloughing) a possible treatment for TEN (Downey, Jackson, Harun & Cooper, 2011). Twelve patients with SJS/TEN received treatment using dexamethasone pulse therapy, administered 1.5 mg/kg/day intravenously for three days. Upon the third day of administration, the disease progression halted and healing began for the following three weeks. According to a prognosis tool known as the SCORTEN, mortality of 4 patients was predicted but resulted in the death of 1 patient that had advanced cancer. Although there was mortality, this particular patient had skin lesions that had totally resolved and healed. Although there are some studies that show the benefits, the use of corticosteroids remains a controversial topic and has been contraindicated due to the increased risk of infection and also because corticosteroids have been listed as a causative drug for the initiation of the TEN disease process (Pereira, Mudgil & Rosmarin, 2007).

**TNFα – inhibitors**

The most classic TNFα – inhibitor is Thalidomide (Pereira, Mudgil & Rosmarin, 2007). A prospective study was terminated due to the increase in mortality in patients that were administered thalidomide. Not only did thalidomide increase the levels of TNFα (Pereira, Mudgil & Rosmarin, 2007) but it was also discovered and determined to be a causative agent for the onset of TEN. Other TNFα inhibitors include infliximab and pentoxifylline. While infliximab revealed beneficial gains, pentoxifylline didn’t have the same results. In fact, only a few TEN patients report benefitting from pentoxifylline. The major drawback with this choice of drug is the concern that the TNFα inhibitors may have “anti-apoptotic effects through the TNF-R1—NF-κB pathway” (Pereira, Mudgil & Rosmarin, 2007).
Intravenous Immunoglobulin (IVIG)

The most recent therapeutic approach to TEN has yielded itself to the use of human intravenous immunoglobulin (IVIGs). It is widely believed that the keratinocytes that become involved during this process are associated with increased keratinocyte FasL expression and interaction with Fas protein on the cell surface. With this increased expression and binding of Fas to its ligand, FasL, it leads to apoptosis of that keratinocyte (Trent, Halem, French & Francisco, 2006). Using its pathophysiology as the rationale for the mechanism of action, IVIG is based on the blockade of the CD95 (Fas) receptor that promotes keratinocyte apoptosis (Lissia, Mulas, Bulla & Rubino, 2009) (Figure 1). Created from the plasma of blood donors, IVIGs are purified until the composition contains 90 to 98 percent IgG and traces of IgA, IgM, CD4, CD8, HLA molecules and cytokines (Lissia, Mulas, Bulla & Rubino, 2009). While IVIG dosage is still unclear, a protocol made recommendations that IVIG should be infused at doses of 0.7 g/kg daily for 4 days with methylprednisolone 250 mg/6h for the first 48h (Viard et al., 1998).

Other sources recommend a dose of IVIG at 1g/kg/day for 3 days (Prins et al., 2003). In between 1997 and 2000, that same study involving 14 European and American university-based dermatology centers, 48 patients received IVIG treatment and supportive care. Of that 48 patient population, the survival rate was 88 percent. In another study, 16 patients were treated with the standard 1g/kg/day IVIG treatment and report only one death compared to the SCORTEN estimation of 5.8 deaths (Trent, Kirsner, Romanelli & Kerdel, 2003). More successful survival rates are reported in other studies.

In a prospective study of 12 TEN patients from Kuwait, a 100 percent survival rate is observed. Another study reported eight of the nine patients surviving after being treated for TEN
with IVIG and pulse methylprednisolone despite the controversy surrounding steroid use in the
treatment of TEN (Al-Mutairi et al., 2004). Overall, this study determined IVIG in the treatment
of TEN a “safe and valid” therapy (Al-Mutairi et al., 2004). Another meta-analysis study from
March 2012 concluded from its study that although there “was no sufficient evidence to conclude
that IVIG provides a clinical benefit in adults”, “high-dose IVIG (total dose ≥ 2 kg⁻¹) had a
positive trend towards improved mortality” (Huang, Li & Chen, 2012).

**Plasmapheresis**

The procedure that removes whole blood volume and separates plasma from other
cellular constituents is known as plasmapheresis (Pereira, Mudgil & Rosmarin, 2007). The
cellular constituents with added albumin or new plasma are reinfused back into the patient.
Plasmapheresis serves to remove “pathogenic, nondialyzable plasma factor, such as a drug,
poison, metabolite, antibody, immune complex, or disease-inducing cytokine” (Pereira, Mudgil
& Rosmarin, 2007). In literature, plasmapheresis is reported with some measure of success in the
treatment of TEN (Egan, Grant, Morris, Saffle, Zone, 1999; Lissia, Mulas, Bulla & Rubino,
2009). Plasmapheresis has even been seen as a conjoined intervention with IVIG in one
particular study. The survival rate associated with this intervention varies from 77 to 100 percent
(Chaidemenos et al., 1997; Yamanda, Takamori, Yaguchi & Ogawa, 1998). Although, positive
results are observed in the majority of studies there are also studies that reveal non-responding
patients that underwent plasmapheresis (Roujeau, Chosidow, Saiag & Guillaume, 1990;
Sakellariou et al., 1991).

Another study showed no difference in survival compared to other groups that were being
treated with solely supportive care (Furubacke, Berlin, Anderson & Sjoberg, 1999). Even then,
the overall survival rate was 87.5 percent. It is still unclear about the role of plasmapheresis in the treatment of TEN. Due to the limited amount of studies done on plasmapheresis in the management of TEN, there remains no agreement about the efficacy of this as a reliable treatment option (Lissia, Mulas, Bulla & Rubino, 2009; Egan, Grant, Morris, Saffle, Zone, 1999).
Prognosis

The degree of epidermal involvement determines the outcome and prognosis for a patient with TEN (Downey, Jackson, Harun & Cooper, 2011). With minimal epidermal involvement, lower mortality rates are reported while increased epidermal involvement is associated with increased mortality rates. The most common cause of death in TEN is infection (Roujeau & Stern, 1994). Fatal complications that are associated with the TEN disease course include pulmonary embolism, adult respiratory distress syndrome, gastrointestinal hemorrhage, cardiac, and renal failure (Mukasa & Craven, 2008). In an effort to measure disease severity and predict mortality, Bastuji-Garin et al. (2000) developed the SCORTEN to use to estimate prognosis.

SCORTEN should be calculated within the first 24 hours after admission and once more on day three. Using the seven clinical variables: 1) age over 40 years; 2) heart rate > 120 beats per minute; 3) the presence of cancer or any other hematologic malignancy; 4) epidermal detachment involving body surface >10% on the first day; 5) blood urea nitrogen (BUN) > 28 mg/dL (10 mmol/L); 6) glucose > 252 mg/dL (14 mmol/L); and 7) bicarbonate < 20mEq/L. One point is assigned for each variable, with worsening mortality per every additional point added (Tables 3 & 4).

Other clinical parameters list thrombocytopenia, leucopenia, delay in hospital admission, and treatment with antibiotics or corticosteroids prior to admission as predictors of mortality as well. The SCORTEN’s accuracy has been proven to accurately predict mortality.
Conclusion

Life-threatening reactions will continue to be a relevant issue and problem due to the constant development and prescribing of new medications. Literature has revealed the importance of discontinuing the causative agent and has stressed the need for intensive supportive care in a burn unit. Although the incidence is low, morbidity and mortality is high. The key to stopping mortality is starting intervention as early as possible. The cornerstone of TEN treatment remains supportive care in a burn unit.

At this time no concrete recommendations concerning specific therapies can be made due to the conflicting data and lack of supportive research to provide sufficient quantitative data. At this point, the use of adjunctive therapy is still a matter of clinical judgment and considered complementary. However, there is sufficient evidence to suggest that the use of steroids should be completely avoided while other therapies such as and high-dose human intravenous immunoglobulin (IVIG) continues to reveal very promising results trending toward improved mortality and prognosis.
References


Tables

Table I. *Incidence of TEN* (Letko et al., 2005).

<table>
<thead>
<tr>
<th>Location</th>
<th>Period</th>
<th>Annual incidence (per 1 million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>1964-1969</td>
<td>0.4</td>
</tr>
<tr>
<td>Seattle</td>
<td>1972-1986</td>
<td>0.5</td>
</tr>
<tr>
<td>United States</td>
<td>1980-1984</td>
<td>&lt;1</td>
</tr>
<tr>
<td>West Germany</td>
<td>1981-1985</td>
<td>0.93</td>
</tr>
<tr>
<td>France</td>
<td>1981-1985</td>
<td>1.2-1.3</td>
</tr>
<tr>
<td>Italy</td>
<td>1984-1988</td>
<td>0.6</td>
</tr>
<tr>
<td>Italy</td>
<td>1989</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Table 2. *Etiology of TEN* (Letko et al., 2005).

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of patients</th>
<th>Drug</th>
<th>Unknown</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porteous and Berger (Lyell, 1956)</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Power et al (Takeda, Mitasuhashi, Kondo, Kato &amp; Tajima, 1997)</td>
<td>30</td>
<td>24</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Villada et al (Egan, Grant, Morris, Saffle, Zone, 1999) (Chan et al., 1990)</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Guibal et al (Egan, Grant, Morris, Saffle, Zone, 1999)</td>
<td>13</td>
<td>9</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>McIvor et al (Downey, Jackson, Harun &amp; Cooper, 2011) (Egan, Grant, Morris, Saffle, Zone, 1999)</td>
<td>12</td>
<td>10</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total No. (%)</strong></td>
<td><strong>63 (100)</strong></td>
<td><strong>48 (76.2)</strong></td>
<td><strong>2 (3.2)</strong></td>
<td><strong>13 (20.6)</strong></td>
</tr>
</tbody>
</table>
Table III. Differential Diagnosis of TEN (Pereira, Mudgil & Rosmarin, 2007).

<table>
<thead>
<tr>
<th>Bullous Disease</th>
<th>Fever</th>
<th>Mucositis</th>
<th>Morphology</th>
<th>IF</th>
<th>Onset</th>
<th>Miscellaneous Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemphigoid</td>
<td>No</td>
<td>Rare</td>
<td>Tense bullae (sometimes hemorrhagic)</td>
<td>+</td>
<td>Acute</td>
<td>Diuretics a common cause, especially spironolactone; often pruritic</td>
</tr>
<tr>
<td>Staphylococcal scalded skin syndrome (SSSS)</td>
<td>Yes</td>
<td>Absent</td>
<td>Erythema, skin tenderness, periorificial crusting</td>
<td>—</td>
<td>Acute</td>
<td>Affects children under 5, adults on dialysis and those on immunosuppressive therapy</td>
</tr>
<tr>
<td>Drug-induced pemphigus</td>
<td>No</td>
<td>Usually absent</td>
<td>Erosions, crusts, patchy erythemaling resemble pemphigus foliaceous)</td>
<td>+/-</td>
<td>Gradual</td>
<td>Commonly caused by penicillimine and other “thiol” drugs; resolves after inciting agent is discontinued</td>
</tr>
<tr>
<td>Acute graft-versus host disease</td>
<td>Yes</td>
<td>Present</td>
<td>Morbilliform rash, bullae and erosions</td>
<td>—</td>
<td>Acute</td>
<td>Self-limiting on discontinuation of drug</td>
</tr>
<tr>
<td>Drug-induced linear IgA bullous dermatosis</td>
<td>No</td>
<td>Rare</td>
<td>Tense, subepidermal bullae (resembles pemphigoid)</td>
<td>+</td>
<td>Acute</td>
<td>Vancomycin most commonly implicated drug; pruritus often present</td>
</tr>
</tbody>
</table>
Table IV. SCORTEN (Bastuji-Garin et al., 2000).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;40 years</td>
<td>Yes =1; No = 0</td>
</tr>
<tr>
<td>TBSA involved &gt;10%</td>
<td>Yes =1; No = 0</td>
</tr>
<tr>
<td>Serum urea level &gt;28 mg/dl</td>
<td>Yes =1; No = 0</td>
</tr>
<tr>
<td>Glucose level &gt;252 mg/dl</td>
<td>Yes =1; No = 0</td>
</tr>
<tr>
<td>Bicarbonate level &lt;20 mEq/l</td>
<td>Yes =1; No = 0</td>
</tr>
<tr>
<td>Heart rate &gt; 120 beats per minute</td>
<td>Yes =1; No = 0</td>
</tr>
<tr>
<td>Presence of malignancies</td>
<td>Yes =1; No = 0</td>
</tr>
</tbody>
</table>

Table V. SCORTEN level and predicted mortality (Pereira, Mudgil & Rosmarin, 2007).

<table>
<thead>
<tr>
<th>SCORTEN</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>3.2%</td>
</tr>
<tr>
<td>2</td>
<td>12.1%</td>
</tr>
<tr>
<td>3</td>
<td>35.3%</td>
</tr>
<tr>
<td>4</td>
<td>58.3%</td>
</tr>
<tr>
<td>5 or greater</td>
<td>90.0%</td>
</tr>
</tbody>
</table>

Each risk factor is assigned one point and the sum of the points assigned from each risk factor determines the final score which is the value of the “SCORTEN”.
Figure 1. *Fas-mediated keratinocyte apoptosis in TEN and potential mechanism of inhibition of IVIG.*

(French, Trent & Kerdel, 2006)

(A) Normal epidermis and (B) toxic epidermal necrolysis: induction of keratinocyte FasL expression and interaction with Fas at the cell surface, leading to keratinocyte apoptosis (C) epidermis during TEN treated by IVIG: predicted inhibition of keratinocyte apoptosis by blockade of Fas by anti-Fas Ab in IVIG (French, Trent & Kerdel, 2006).
Figure 2. *TEN: Blistering and epidermal sloughing characteristic of toxic epidermal necrolysis.*

(Downey, Jackson, Harun & Cooper, 2011)

A: Lesion 1 day after admission with positive Nikolsky sign. B: Widespread epidermal loss with erythematous areas of expansion 3 days following admission. This patient progressed to have more than 90% total body surface area involved.
Figure 3. Histologic appearance of TEN. (Pereira, Mudgil & Rosmarin, 2007)

Epidermis shows confluent necrosis and separation from the dermis. Within the dermis there is a sparse infiltrate consisting mainly of lymphocytes. Note the reepithelialization occurring as the necrotic keratinocytes are shed. (Hematoxylin-eosin stain; original magnification: X20.)
Figure 4. *Apoptosis induced by perforin/granzyme B.* (Pereira, Mudgil & Rosmarin, 2007)
Abstract

Background: Toxic epidermal necrolysis (TEN) is a severe life-threatening condition associated with a low incidence but high mortality rate ranging from 25-50%. TEN is characterized by its widespread skin necrosis with frequent mucous membrane involvement. The pathophysiology of TEN has yet to be fully understood, however the current understanding involves a limited scope.

Objective: Realizing the importance of recognizing and treating such a condition for the practicing clinician in the world of medicine and dermatology, we have performed a comprehensive review to enhance the understanding of its presentation and treatment.

Methods: A search was conducted using PubMed, Science Direct, and Google Scholar search engines at the Mulford Library of the University of Toledo from inception to September 2012. All articles used in the composition of this project were review articles and clinical human studies written in English. The search parameters included the terms ‘toxic epidermal necrolysis’, Lyell’s syndrome’ or ‘toxic epidermal necrolysis’ combined with ‘IVIG’ or ‘intravenous immunoglobulin’. Publication date parameters were set to include all years between 1990 and 2012.

Results: Serious complications such as respiratory failure and infections are among the feared outcomes therefore treatment is done in a specialized burn unit with a multidisciplinary team involved. We have found that steroid use should be completely avoided and that performing skin biopsy is crucial to the diagnosis and helps to rule out any other diagnoses.

Conclusion: The value of current therapies such as intravenous immunoglobulins (IVIGs) reveals very promising results trending toward improved mortality and prognosis however quantitative analysis of this treatment is lacking and yet to be determined by further research.