Toxic Epidermal Necrolysis

Subjects: Critical Care Medicine

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Toxic Epidermal Necrolysis is a rare dermatological condition with high mortality and serious consequences on its survivors. Despite having been first described in 1956, its pathophysiology remains uncertain, mainly regarding its mechanisms, although it seems that certain apoptosis pathways are pivotal in starting keratinocytes' apoptosis and in activating T cells, especially those mediated by tumour necrosis factor, Fas-FasL and granulysin. In general, its aetiology and presentation are consensual, being defined as a generalized necrolysis of the epidermis that occurs as an uncontrolled immune response to a specific drug or one of its metabolites, highlighting cotrimoxazole and allopurinol as the most important. This necrolysis leads to a massive shedding of the epidermal layer of the skin, with stronger incidences in the torso, upper limbs and face. Its complications tend to be severe, noting that septic ones are responsible for over half of the disease's mortality. Nearly all survivors develop long-term sequelae, namely hypertrophic scarring and skin pigmentation anomalies.

Keywords: toxic epidermal necrolysis ; Lyell's syndrome ; ALDEN ; TNF ; IVIG ; SCORTEN

1. Introduction

Toxic Epidermal Necrolysis (TEN), also known as Lyell's Syndrome, is a rare dermatological condition of great clinical severity [1][2][3]. It was described for the first time in 1956 by Alan Lyell [4], after whom it was named, and in most cases, it derives from the exposure to certain drugs, accounting for 1% of all hospitalizations for adverse drug reactions [1]. Regarding its clinical features, TEN is characterized by generalized mucocutaneous necrolysis, with bullous lesions and epidermal detachment affecting more than 30% of total body surface area (TBSA) [3][5][6]. This syndrome is rare, with an annual incidence of 1–2 cases per 1,000,000 people [1]. Its mortality is rather high, varying from 25% to 35% [5] but reaching 50–70% [2] depending on sources. TEN's pathophysiology is not fully understood, and there are several theories suggesting autoimmune mechanisms that may lead to keratinocyte apoptosis and necrosis. However, it is known that this immune response is cell-mediated, namely, by T cells [1][2][6][7]. A few theories propose cellular apoptosis mechanisms to be involved, especially those of Tumour Necrosis Factor (TNF), Fas-FasL and granzymes such as granulysin [1][6][7][8]. In the literature, it is consensual that, in order to achieve the best therapeutic conditions and to ensure the maximum survival rates, patients should be preferentially admitted and treated in Burns Units. As of writing this entry, and despite several new treatment modalities having been studied and proposed, particularly immunomodulation, the only treatment for which its efficacy has been proven and that is widely used is the one built on general support care. However, studies on these new treatments need larger and more representative populations in order to be statistically significant [1][3][7][9][10][11]. TEN is an important study subject, with considerable potential for new discoveries. With this entry, the authors mean to review and summarize information and scientific evidence available. During the study, not only converging points amongst several authors were noted but many interesting targets for research were also referred regarding its pathophysiology and its therapeutic approach. There are still some controversies and disagreements that need better clarification in order to optimize patients' management and outcome.

2. Epidemiology

TEN has a global annual incidence of 1–2 cases per 1,000,000 people. Its mean mortality ranges from 25% to 35%, possibly reaching 50–75% if it is not correctly managed [1][2][5][6]. This syndrome represents about 1% of all hospitalizations for adverse drug effects [1]. TEN has a 1.000-times-higher incidence in HIV-positive individuals, reaching a global annual incidence of 1 case per 1.000 people in these patients [3]. Although it is not restricted to any specific age group, it is more common at age extremes: before 5 years and after 64 years of age. It also affects more women than men in a proportion of 2:1 or even 3:1 [1].

3. Aetiology

In most cases (80–85%), the origin of TEN is tethered to an idiosyncratic reaction to a dose-independent exposure to certain pharmacological groups [1][2][6], but it is important to note that there is a small percentage of patients that develop TEN by unknown non-pharmacological mechanisms [12]. Over 220 drugs have been linked to TEN, with higher or lower frequencies [3][5]. As there is no trustworthy test that conclusively proves a specific drug's causality, it is safer to speak only of a suspect or probable drug as the causal agent [3]. To evaluate the risk of occurrence of TEN, an Algorithm of Drug Causality in Epidermal Necrolysis (ALDEN) was created, for which its use has been validated as a reference tool [6] (**Table 1**).

Table 1. Algorithm of Drug Causality in Epidermal Necrolysis (ALDEN) [12].

Criteria	Value		Rules of Application
Latency between drug administration and onset of symptoms (index day)	Suggestive	+3	From 5 to 28 days.
	Compatible	+2	From 29 to 56 days.
	Probable	+1	From 1 to 4 days.
	Improbable	−1	More than 56 days.
	Excluded	−3	Drug administered on index day.
	NOTE: If there is a previous reaction to the same drug, it is considered "suggestive +3" from 1 to 4 days and "probable +1" from 5 to 56 days.		
Probability that the drug was present in the patient's system	Definitive	+0	Drug administered until index day or stopped less than 5 elimination half-lives before index day.
	Doubtful	−1	Drug stopped more than 5 elimination half-lives before index day, with abnormal renal and/or hepatic functions or suspected pharmacological interactions.
	Excluded	−3	Drug stopped more than 5 elimination half-lives before index day, with normal renal and hepatic functions and no pharmacological interactions.
Prechallenge or rechallenge	Positive specifically for disease and drug	+4	Occurrence of SJS/TEN [1] after the use of the same drug.
	Positive specifically either for disease or drug	+2	Occurrence of SJS/TEN after the use of a similar drug or another adverse reaction to the same drug.
	Positive non-specifically	+1	Occurrence of another adverse drug reaction to a similar drug.
	Unknown/not performed	+0	No knowledge of previous exposure to the drug.
Dechallenge	Negative	−2	Previous exposure to the drug without any adverse reaction of any kind.
	Neutral	+0	Drug stopped or unknown.
	Negative	−2	Drug not stopped without worsening of clinical condition.
Drug notoriety	Strongly associated	+3	High risk drug.
	Associated	+2	Lower but proven risk drug.
	Suspect	+1	Ambiguous epidemiology; drug "under surveillance".
	Unknown	+0	All other drugs, including new ones.
	Not suspect	−1	No evidence of association.
INTERMEDIATE SCORE = −11 to +10			Sum of all previous criteria.
Other possible aetiologies for the symptoms?	Possible	−1	List all other administered drugs according to their intermediate score and if at least one > 3.

[1] Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis.

This algorithm allows an individual assessment of drug causality, potentially reducing treatment costs and informing the patient about which drug is contraindicated from then on. This algorithm is specific for epidermal necrolysis, encompassing SJS and TEN, and measures six parameters: (1) time spent between drug intake and onset of reaction (index day); (2) probability that the drug was present in the patient's system at the onset of reaction; (3) prechallenge or rechallenge, which are the occurrence of any adverse reactions to a prior administration or a subsequent administration of that specific drug; (4) dechallenge, i.e., an improvement of the patients clinical status after the drug's removal; (5) drug notoriety; and (6) other possible etiological alternatives. ALDEN should be calculated for every single drug known to be taken by the patient, ranging from −12 to +10. Its application distributes drugs into five different categories (**Table 2**): very probable (≥6); probable (4 to 5); possible (2 to 3); unlikely (0 to 1); or very unlikely (<0) [12].

Table 2. ALDEN score interpretation [12].

Final Score	Classification
<0	**Very unlikely**
0–1	**Unlikely**
2–3	**Possible**
4–5	**Probable**
≥6	**Very probable**

Amongst the many pharmacological groups that have been linked to TEN (**Table 3**), the most frequent are the following: sulphonamides, especially cotrimoxazole, that represent nearly 33% of all cases in adults; antiepileptics such as phenytoin, the most frequent in paediatric ages, carbamazepine and phenobarbital; allopurinol; oral penicillin; non-steroid anti-inflammatory drugs (NSAIDs) with long half-life, namely pyrazolone and the oxicam group; and, more recently, nevirapine and lamotrigine [1][3][5][6][7][9].

Table 3. Highrisk drugs for the development of TEN [3][5][6][13].

Pharmacological Group	Strong Association	Less Strong Association	Weak Association
Antibiotics	**Sulphonamides (especially cotrimoxazole)**	**Amoxicillin**	**Nitrofurantoin**
		Cephalosporines	**Vancomycin**
		Macrolides	
		Quinolones (typically, ciprofloxacin)	
		Tetracyclines	
Antiepileptics	**Carbamazepine (mainly in paediatric ages)**		**Valproate**
	Lamotrigine		
	Phenobarbital		
	Phenytoin		
Analgesic and anti-inflammatory drugs	**NSAIDs [1] from 'oxicam' group**	**Acetic acid NSAIDs (e.g., diclofenac)**	**Acetaminophen (paracetamol)**
		Ibuprofen	**Tramadol**
Antidepressants		**Sertraline**	**Fluoxetine**
			Mirtazapine
Other	**Allopurinol**	**Pantoprazol**	**Diltiazem**
	Sulfasalazine		
	Nevirapine		

[1] Non-steroidal anti-inflammatory drugs.

However, there are confounding factors that may impact the identification of a causal drug. For example, oral penicillin, acetaminophen (paracetamol) and corticosteroids are usually administered to treat non-specific symptoms that can be premature ones of TEN [12][13]. The risk of development of TEN is usually limited to the first two months of treatment [7][12], and the first three weeks are the most critical [3][9]. For this reason, it is considered that a previous exposure to a specific drug with no adverse reactions diminishes the probability of that drug being the culprit [12].

4. Pathophysiology

TEN remains an important study target given that its pathophysiology is not fully understood. The scientific community agrees that, in its core, there is an immunological mechanism mediated by cytotoxic T cells. These cells are the most frequently found in inflammatory infiltrates of desquamative areas and in bullous fluids [1][2][6]. T cells have, in fact, a granulysin-mediated cytolysis mechanism [6][8]. However, the reasons why this immune system's unregulated response occurs are still uncertain. The main mechanism is the massive apoptosis of keratinocytes supported by the identification of several receptors of apoptosis pathways on their cell membranes, more importantly the TNF, Fas-FasL and TRAIL groups [2]. This apoptosis process is mediated essentially by Fas-FasL and perforin-granzyme B [8][14], which can be overactivated by the presence of a specific drug or one of its metabolites. The response is then amplified by inflammatory cells, mainly CD^{8+} T cells and soluble inflammatory mediators [14]. It is thought that TNF-α, which can be secreted by macrophages and by keratinocytes, may have a fundamental role in TEN, either by recruiting cytotoxic cells or by inducing the apoptosis of keratinocytes. This molecule was identified in epidermal samples of TEN patients and also in fluids collected from bullous lesions and peripheral blood. Notwithstanding, TNF's role is not yet clarified as it could have a proapoptotic or antiapoptotic effect in TEN. A few studies have shown that thalidomide (an immunomodulating anti-TNF drug) may have a deleterious effect on these patients, increasing their mortality. This seemingly supports the theory that TNF could play an anti-apoptotic role in TEN. Objectively, increases in TNF and FasL levels were observed in TEN patients, but these mechanisms are unspecific and present in other pathologies, thus not explaining why some patients develop TEN and suggesting that there may be a rare polymorphism that alters their functions in controlling apoptosis [2].

Another accepted theory is known as "p-i Concept". It is based on a direct interaction between drugs and class I Major Histocompatibility Complexes (MHCs) that triggers hypersensitivity reactions mediated by CD^{8+} T cells, with granulysin-controlled cytolysis [6]. According to this theory, the culprit drug sets in motion an immune response mediated by MHC, with the clonal expansion of CD^{8+} T cells and interleukin-2 (IL-2) secretion, followed by keratinocyte apoptosis that can occur in two phases: one guided by T cells, as it happens in other dermatological adverse drug reactions, and that is highly dependent on granulysin and cellular death pathways; and another with response amplification that is specific to TEN [2].

Granulysin is a cytolytic protein that may have a key role on TEN's pathophysiology. Its levels in skin biopsy samples surpassed all other cytolytic proteins, such as granzyme-B, perforin and FasL [8]. Additionally, its mechanism appears to be specific to SJS/TEN, and its levels are directly linked to clinical severity [8][15]. The secretion of granulysin in high levels by T cells, Natural Killer (NK) cells and Natural Killer T cells (NKT) leads to undue apoptosis and tissue damage, which appears to culminate in these patients' typical clinical presentation. Granulysin also operates as a chemotactic agent and activates pro-inflammatory molecules. High concentrations of this molecule in the extracellular space of necrotic and bullous lesions are a probable cause of the rapid development of epidermal necrolysis observed in TEN [8]. It is known that IL-15 increases granulysin secretion [15], and it is possible that granulysin is potentiated by the remaining cytotoxic molecules, causing a synergic effect that worsens keratinocyte apoptosis. Measuring granulysin levels in liquid collected from bullous lesions may be a useful tool in differential diagnosis and an important biomarker for evaluating disease progression [8].

The implication of drug metabolism in TEN is not clear; however, some metabolites, namely hydroxylamine derived from sulphonamide or aromatic antiepileptics, quickly bind to cells if they are not properly removed by epoxide hydroxylase. These metabolites become antigenic when displayed on cell surfaces and can activate apoptosis pathways [6].

In spite of the extreme rarity of a second episode of TEN, the observation of a reduction in latency between drug exposure and clinical onset in a recurrence (from 12–14 days to only 2 days) suggests that there may be a primary sensitivity mechanism and immunological memory [6]. In fact, it is relatively common that TEN survivors develop autoimmune diseases such as Systemic Lupus Erythematous (SLE) or Sjögren's Syndrome [1][6].

5. Clinical Presentation

Drug exposure is usually followed by a prodromal period, with unspecific symptoms (fever, myalgia, malaise, anorexia and asthenia) or even rhinitis, cough and chest pain. These symptoms can last between 1 and 14 days [1][2][5][6]. The first mucocutaneous symptoms begin to appear abruptly 2 to 3 days after the prodromal period, initiating the acute phase, which can last from 2 to 12 days. Generalized pruritus is commonly the first manifestation, but it is rapidly followed by painful eruptions that appear mainly in the face and torso, despite possibly spreading centrifugally towards the remaining body parts in just a few days. The most frequently affected areas are the torso and proximal upper limbs [1]. The initial lesions are erythematous macules, with irregular borders and a darker central region (target-like), reaching its maximum size in 2 to 3 days depending on the culprit drug's half-life [1][6][13][14]. These macular lesions coalesce and quickly turn into bullous ones, with clear fluid, creating great plaques of necrotic epidermis. Keratinocyte necrosis takes place essentially in the spinous and basal layers of the epidermis, which detaches cleanly off the dermal layer and remains intact albeit exposed [1][6]. The loss of the epidermis is accompanied by the detachment of fingernails and a loss of eyebrows [15]. At supposedly healthy areas, a slight smear pressure may trigger the shedding of the epidermis; this is called Nikolsky's sign, which is an important tool for differential diagnoses [1][2][3][5][6][13]. A triad can be defined for TEN comprising mucosal eruptions, epidermal necrosis with desquamation and target-like lesions [5]. Epidermal necrolysis can involve the entire body, generally sparing the scalp [1][7], and the total loss of the epidermis in less than 24 h is not uncommon [3]. Desquamative areas are identifiable by their exudative and dark-red dermis. Epidermal detachment leads to fluid, protein and electrolyte losses, similarly to burn patients, and if it is not properly mitigated, it will induce serious hydroelectrolytic and haemodynamic disorders, most importantly dehydration, hypovolemia and acute renal failure [1]. Mucosal lesions are observed in more than 90% of cases and usually precede epidermal necrolysis by 1 to 3 days [3][7][14]. These are mainly erosive, with a loss of conjunctival, oropharyngeal, nasal and/or oesophageal mucosae, or even urethral, anal, vaginal and/or perineal, suggesting a predilection for stratified squamous epithelium [1][6][9]. The extension and the localization of these mucosal lesions is variable and specific to every patient, but they are always painful and can compromise a correct hydration and nutrition routine. Early ocular involvement is extremely relevant, and it is found in almost every patient with TEN and can cause photophobia [1]. Some authors propose that a patient with extensive cutaneous erythema and ocular involvement may safely be assumed as a victim of TEN and, inversely, the absence of ocular involvement almost rules out this diagnosis [9]. Urethral lesions can lead to the urinary retention and necrosis of renal tubules, which, along with hydroelectrolytic disorders, can negatively impact the therapeutic approach to these patients [1][13]. The body's temperature may remain high throughout the entire acute phase, even without infectious complications. This could be due to the release of endogenous pyrogenic agents by necrotic tissues, especially IL-1 [1].

The most serious complication that frequently leads to death is infection. Sepsis is the main cause of TEN-associated mortality [1][3][6][14][16], accounting for more than 50% and surpassing non-septic multiorgan failure [1][14]. This complication is greatly facilitated by the loss of the epidermal barrier, facilitating the invasion of tissues by bacteria and other microbes from the skin [1][16]. Contrarily to thermic burns, in TEN, the dermis remains intact, although it is still susceptible to invasion by microorganisms that multiply freely in exudates and necrotic epidermis [1]. Cutaneous lesions in TEN, similarly to burns, are primarily colonized by *Staphylococcus aureus* and then followed by Gram-negative bacteria that mainly come from the patient's digestive tract, notably *Pseudomonas aeruginosa* [1][3][16]. Patients under previous treatment with broad spectrum antibiotics can also develop fungal infections, most frequently by *Candida albicans* [1]. Around 25% of patients will suffer from hematological dissemination (bacteraemia) either by *S. aureus*, *P. aeruginosa* or Enterobacteriaceae. Upon the date of admission, there are certain variables that, when present, help clinicians in predicting the risk of bacteraemia and sepsis: age over 40 years-old; leucocytosis over 10.000/mm3; and an affected TBSA of 30% or higher. The identification of colonization by meticilino-resistant *S. aureus* (MRSA) or *P. aeruginosa* in skin cultures is predictive of bacteraemia by the same microorganisms. Its peak incidence is attained after around 11 days after the onset of symptoms or about 5 days after hospitalization [16], and it is greater in patients with central venous catheters (CVC). In some cases, sepsis in TEN can lead to Disseminated Intravascular Coagulation (DIC) [1]. The high prevalence of bacteraemia associated with Enterobacteriaceae strengthens the theory that these patients may experience digestive bacterial translocation [16]. Besides its haematogenic origin, starting from cutaneous lesions or intestinal translocation, sepsis could also develop as a consequence of pneumonia [14].

Multisystemic involvement is relatively common in TEN [9]. Ocular complications are frequent, affecting nearly 74% of patients [3], and they can vary from light conjunctival hyperaemia to the formation of pseudomembranes with the fusion of the eyelid to the ocular globe (symblepharon) which can lead to complete blindness [1][3][6]. These lesions are due to the erosion and desquamation of the conjunctival mucosa, with consequent fibrosis [1][6]. Nevertheless, the most frequent ophthalmological complications are photophobia, xerophthalmy and foreign body sensations [7]. Respiratory disfunctions are a common finding present in 25–30% of patients [3][9], and they can require invasive mechanical ventilation in 10–20%, even without radiographical anomalies [7][14]. Some disturbances can be found through optical bronchofibroscopy.

These disfunctions can accrue from several factors, such as superficial breathing caused by pain or pulmonary oedema from increased alveolar–capillary permeability [1]. Additionally, the aspiration of debris of oropharyngeal mucosa can also lead to aspiration pneumonia and bronchiolitis obliterans or even acute respiratory distress syndrome (ARDS) [1][2]. Respiratory difficulties settle in progressively and can go unnoticed, but they can be hinted at by the onset of dyspnoea, tachypnoea and marked hypoxemia [3][7][9]. Its treatment includes saline nebulisations, bronchodilators, respiratory physiotherapy and, when needed, invasive mechanical ventilation. The use of non-invasive mechanical ventilation is not recommended seeing that the pressure and friction associated with facial masks can aggravate perioral and perinasal desquamation. Respiratory failure is a sign of a poor prognosis [2]. Besides oropharyngeal mucosal destruction, gastrointestinal involvement encompasses the appearance of distal erosions, namely at the oesophagus, resembling peptic oesophagitis. These lesions may, in rare occasions, lead to dysphagia and gastric bleeding. Intestinal lesions are less frequent and can be evidenced by haematochezia. Although close to 50% of patients present with rising hepatic transaminases (AST and ALT), only about 10% will develop hepatitis. Haematological disorders are also very common, particularly anaemia, which is usually normocytic and normochromic and could be precipitated by diverse reasons, including erythroblastopaenia. Leukopenia is relatively frequent, with lymphocytopenia occurring in 90% of TEN cases, which can be explained by the depletion of CD^{4+} T cells; on the other hand, neutropenia is found in 30% of patients and is, generally, associated with sepsis. However, it is uncertain if neutropenia is either caused by medullary disfunction or solely as a secondary idiopathic phenomenon. Thrombocytopenia is the least frequent of the cytopenias and it arises in 15% of cases [1][2].

After its acute phase, the chronic phase begins and this is where long-term sequelae stand out, as they occur in nearly 90% of survivors after 1 year [17]. The most common sequelae are: (1) dermatological, namely dryness of skin, pigmentation anomalies, nail defects, alopecia and alterations of the sudoriferous pattern [1][7][17]; (2) ophthalmological, such as xerophthalmia, cicatrising conjunctivitis, lagophthalmos and symblepharon, which affect visual acuity on various levels, even possibly leading to total blindness; (3) oral, including xerostomia and dental defects; (4) genital, more prominently phimosis in men [7][17]; and, rarely, (5) gastrointestinal and (6) bronchial. It is also important to emphasize the psychological sequelae, mainly post-traumatic stress disorder (PTSD), which can seriously impact the efficacy of future treatments, given the fear of a new TEN [17].

6. Diagnosis

TEN can be presumed from typical clinical signs, with at least three of the following present: disseminated purpuric maculae or target-shaped lesions; epidermal desquamation; multifocal mucosal erosions; and positive Nikolsky's sign [17]. However, a definitive diagnosis requires a skin biopsy and its histological analysis [1][5][6][17]. The biopsy should be performed as early as possible and also allows the exclusion of differential diagnoses, which benefit from targeted, specific and distinct treatments [7]. The general rule is that two specimens should be collected for anatomopathological analysis: one for routine evaluation with haematoxylin-eosin and another for direct immunofluorescence [5]; there is yet another preparation, Tzanck smear, that can reveal eosinophils and basal cells with an elevated nucleus/cytoplasm ratio [1][4]. From an anatomopathological point of view, the lesions are characterized by total epidermal depth keratinocyte necrosis, with subepithelial bullae and basal membrane vacuolization [1][4][14]. In its initial stages, a predominantly T cell-populated dermal infiltrate is frequently found [3][9][17], but a prompt switch to a macrophage infiltrate can occur [9]. Chung et al. [8] proposed that measuring granulysin levels in bullous lesions' fluid could be an alternative to skin biopsy as a definitive diagnosis exam; however, the latter remains as the gold-standard exam for TEN.

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