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An update on diagnosis and treatment of toxic epidermal necrolysis

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Abstract

Toxic epidermal necrolysis is an idiosyncratic drug reaction which manifests with extensive epidermal detachment due to the massive keratinocyte apoptosis, mucous membrane involvement, and potentially lethal outcome. It is caused by adverse reactions to drugs, mostly idiosyncratic, unpredictable and independent of the applied dose, which develops 7-21 days after initiation of the drug, and is most commonly caused by the following drugs: sulfonamides, allopurinol, carbamazepine, phenobarbitone, phenytoin and oxycam group of nonsteroidal anti-inflammatory drugs. The treatment outcome depends on several factors, while older age, multiple drug use, late exclusion of the drug inducing toxic epidermal necrolysis, raised serum levels of urea, creatinine and cytopenia are poor prognostic indicators which are rated in SCORTEN scoring which proved to be of great help in the assessment of disease outcome. The basic approach to the treatment is early diagnosis, immediate suspension of the probable inducing drug, and emergency transport to the closest burn center, since treatment in burn units is associated with a lower risk of infection and mortality of these patients. Exclusion of the drug that induced toxic epidermal necrolysis, and supportive therapy, is the first and only therapy for which there is a consensus in different centers. Various forms of adjuvant therapy are also applied: in France, supportive therapy is a standard of care, in Germany it is short-term use of high-dose corticosteroids, while in USA, in the last decade high-dose intravenous immunoglobulins are the most widely accepted treatment modalities. Case reports and small patients' series described therapeutic effects of plasmapheresis, cyclosporine and other immunosuppressants. In conclusion, elimination of the possible causal agent, rapid transport to the burn unit, and multidisciplinary approach to treatment are of utmost importance for favorable outcome of the disease with 20-30% mortality rate. An update on diagnosis and the treatment of toxic epidermal necrolysis is provided in this review.

Key words

Epidermal Necrolysis, Toxic + diagnosis + therapy + etiology + epidemiology; Drug Toxicity; Signs and Symptoms; Disease Progression; Mortality; Prognosis

Toxic epidermal necrolysis (TEN) is an idiosyncratic drug reaction which manifests with extensive epidermal detachment due to the massive keratinocyte apoptosis, mucous membrane involvement, and potentially lethal outcome (1, 2). TEN belongs to the clinical spectrum of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and it is the most severe form of the disease, whereas distinction of these two entities relies on certain criteria – primarily on severity and percentage of body surface and mucous membrane involvement (Table 1).

Historically, toxic epidermal necrolysis and Stevens-Johnson syndrome were described within the clinical spectrum of erythema multiforme, where Stevens-Johnson syndrome was a member of a spectrum of *erythema multiforme major*. Although final consensus has not been reached, nowadays most authors consider these two entities to be separate (1-5).

Ruskin first described a condition similar to toxic epidermal necrolysis in 1948, whereas a Scottish dermatologist Alan Lyell first described 4 cases of acute exanthema with mucous membrane

Table 1. Clinical spectrum of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

	SJS	Overlap SJS/TEN	TEN
Primary lesion	Purple erythematous livid atypical target lesions	Purple erythematous, livid atypical target lesions	Poorly delineated erythematous plaques, spontaneous or friction-induced epidermal detachment
Distribution	Single, isolated lesions with confluence on the face	Single, isolated lesions, with confluence on the face and trunk	Single, isolated lesions, with confluence on the face, trunk and extremities
Mucous membrane involvement	Yes	Yes	Yes
Systemic symptoms	Sometimes present	Always present	Always present
Percentage of BSA involvement with epidermal necrolysis	< 10	10- 30	>30

Modified according to French LE (5); BSA, Body surface area; SJS, Stevens-Johnson Syndrome; TEN

involvement in 1956, so the disease was named after him – Lyell's disease (4). Lyell combined the main clinical feature – epidermolysis and necrosis – the main histopathological features. Out of 4 described, 2 patients in fact had staphylococcal scalded skin syndrome (SSSS), so the author believed that the disease was caused and mediated by bacterial toxins, so he named it – toxic (4). Nowadays, even though the diagnosis of TEN is mostly clinical, skin biopsy with histopathological analysis has an important role in differential diagnosis of these two diseases, especially in pediatric population.

Epidemiology, etiology and pathogenesis

Toxic epidermal necrolysis is caused by adverse reactions to drugs, mostly idiosyncratic, unpre-dictable and independent of the applied dose. The estimated annual incidence of SJS is 1.6-6/10^6, and of TEN it is 0.4-0.6/10^6. It is more common in women (female to male ratio of 1.5: 1), whereas the risk increases with age. TEN usually begins 7-21 days after initiation of the drug, although, very rarely, it may occur before the 7th day, but also after 28 days from taking the medication. In most cases, it is only possible to set the suspicion that a certain drug induced adverse reactions, because exposure testing is contraindicated in this group of patients. Furthermore, a common problem is the use of several medications simultaneously before the onset of reaction. For particular drugs, such as lamotrigine and carbamazepine, in vitro lymphocyte transformation assay has proven useful in identifying the drug which causes the reaction (6). Sassolas and associates constructed an algorithm (ALDEN) for assessment of Drug Causality in Epidermal Necrolysis, but this algorithm needs confirmation in larger studies (7). Except for drugs, cases of TEN after vaccination, exposure to industrial chemicals and fumigants have rarely been described, as well as extremely rare association with *Mycoplasma pneumoniae* infection (1-5).

More than 200 different drugs have been reported to cause TEN (Table 2), whereas in a large international study, conducted in 6 European cities (EuroSCAR), the following drugs showed significant association with the development of

Table 2. Drugs inducing toxic epidermal necrolysis

Group	Primarily involved drugs
Sulfonamides	(primarily trimethroprim/sulfamethoxazole)
Antibiotics	Aminopenicillins
	Cephalosporins
	Macrolides
	Quinolones
	Tetracyclines
Anticonvulsants	Carbamazepine
	Phenobarbitone
	Phenytoin
Nonsteroidal anti-inflammatory drugs	Oxycams
Other	Nevirapine
	Abacavir
	Alopurinol

*Modified according to Tartarone A. and Lerose R.

TEN: sulfonamides, allopurinol, carbamazepine, phenobarbitone, phenytoin and oxycam group of nonsteroidal anti-inflammatory drugs, as well as new drugs nevirapine and lamotrigine (8).

Bearing in mind that TEN is an idiosyncratic reaction to drugs, it can affect anyone, but it is likely that certain individuals may have a genetic predisposition, as is the case with a higher incidence of HLAB12 in patients with TEN, HLA*B5801 in patients with SJS/TEN reaction to allopurinol, and HLA*B1502 in patients with drug reactions to carbamazepine in different populations (9-11). An increased risk of developing TEN was reported in persons with reduced acetylating capacity (slow acetylators), in immunocompromised (HIV infection and lymphoma), and in individuals with brain tumors, undergoing radiotherapy and receiving anticonvulsants (5, 12).

The period of 1-3 weeks after initiation of drug therapy, which represents a refractory period before the development of TEN, shows that a specific immune response is responsible for the development of the disease. In subjects who previously had SJS/TEN reaction, this period is significantly shorter. The pathogenic substrate of toxic epidermal necrolysis is a massive, drug-induced apoptosis of keratinocytes, activated by drug-specific CD8+ cytotoxic lymphocytes (not by its metabolites, as previously assumed). The existence of drug-specific cytotoxic CD8+ lymphocytes was reported in two studies (13, 14). Presence of CD8+ T-lymphocytes expressing cutaneous lymphocyte antigen (CLA), responsible for skin homing, is already evident in the early stages of TEN (13, 14). It has been demonstrated that cytotoxicity of T-cells in TEN is mediated by

the granzyme, which causes programmed cell death by activating procaspase-8 and perforin, leading to formation of pores in the cells being in contact with T-lymphocytes (13-15). An increased expression of IL-6, TNF-α, IL-18, interferon-γ and FasL was reported in TEN lesions, originating from T-lymphocytes, monocytes/macrophages and keratinocytes (5, 16). Presence of these cytokines is responsible for general symptoms associated with the disease, while increased FasL expression on the surface of keratinocytes, probably induced by interferon-γ is responsible for massive apoptosis of keratinocytes by interaction with Fas molecule, which is constitutively expressed on the surface of keratinocytes (5, 17, 18). Except for the FasL expression on keratinocytes, presence of soluble FasL in the serum of patients with TEN was reported, showing its ability to induce apoptosis of normal keratinocytes (19). Increased concentration of IL-10 was also established, which probably has a role in the termination of an immune response.

Clinical manifestations

Toxic epidermal necrolysis begins with general symptoms: fever, shivering, sore throat, fatigue, cough, sometimes diarrhea and vomiting. This prodromal phase mimics acute respiratory infection and lasts 48-72 hours (rarely up to 7 days), after which generalized macular exanthema develops, with dark erythematous livid maculae of irregular borders, target-shaped with darker centers or bright red maculae with central bullae, which generally become confluent as they spread into great areas of erythema with epidermal detachment and positive Nikolsky sign (Figures 1 and 2). The detached epidermis on the surface of the skin resembles wet cigarette paper which peels away easily, so it is necessary to reduce the patient's movement to a minimum. First symptoms occur at the same time on the trunk, proximal extremities and face, later spreading to the neck, hands and soles, while in most patients, lower extremities are less involved. In less than 24 hours, extensive detachment of the epidermis may involve large skin areas.

Simultaneously, or sometimes a few days after the skin involvement, symptoms affect the mucous membranes of the eyes, nose, mouth, urethra, genitalia, gastrointestinal and mucous membranes of the lower respiratory tract (Figure 2 and 3). Mucous membranes of the eyes, nose, mouth, and genitalia are involved

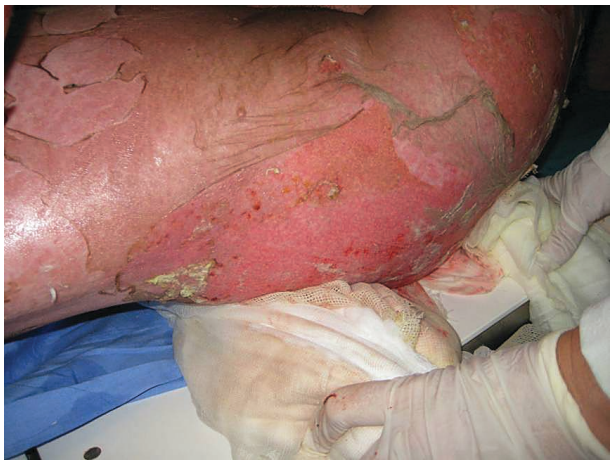

Figure 1. Widespread epidermal detachment resembling wet cigarette paper on the buttocks

in >90% of cases. Ocular manifestations may include purulent and pseudomembranous conjunctivitis, sometimes with erosions or corneal ulcerations, whereas oral lesions mostly occur along the lip vermilion. Involvement of respiratory mucous membranes is registered in 30% of cases, causing bronchial epithelial detachment and development of hypoxemia. In some cases, esophagitis, rectal hemorrhage, vomiting and diarrhea are the consequence of gastrointestinal tract mucous membrane involvement. Common systemic manifestations of the disease include hepatitis, leukopenia, thrombocytopenia and anemia, as well as elevated serum amylase (1-5, 20).

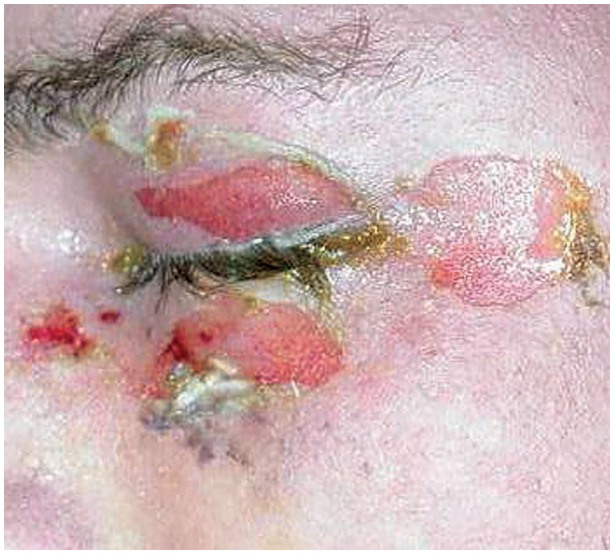

Figure 2. Erosions around the eyes with conjunctival eroisons and secretion

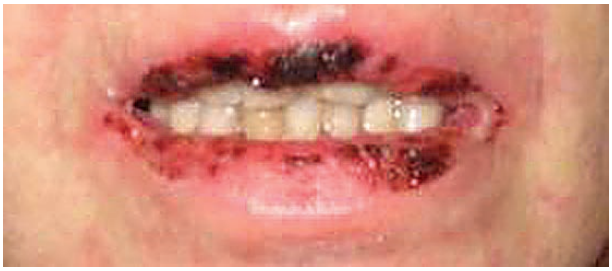

Figure 3. Healing erosions covered with hemorrhagic crusts on the lips

Massive transepidermal fluid loss leads to electrolyte imbalance with prognosis of hypoalbuminemia, insulin resistance, hypercatabolic state, with increased risk for disseminated intravascular coagulation. A compromised skin barrier function increases the risk of sepsis, mostly caused by *Staphylococcus aureus* or *Pseudomonas aeruginosa*, which are the most common causes of lethal outcome in patients with TEN (21).

Diagnosis, differential diagnosis and disease severity assessment

The diagnosis of toxic epidermal necrolysis is primarily based on the typical clinical symptoms, but skin biopsy is necessary for histological analysis and direct immunofluorescence test.

Histopathological analysis shows subepidermal cleavage with confluent keratinocyte necrosis of the whole epidermis and slightly pronounced perivascular lymphocytic infiltrate in the dermis (Figure 4). Rapid histopathological diagnosis is based on the analysis of cryostatic skin sections. Immunohistochemically, lymphocytes present in the epidermis are $CD8^+$, whereas those in the papillary dermis belong to $CD4^+$ subpopulation. Direct immunofluorescence analysis is important for differential diagnosis of TEN and autoimmune bullous dermatoses, some also drug-induced, as well as of lupus erythematosus (Table 3.). Based on clinical findings and massive necrosis of

Table 3. Differential diagnosis of toxic epidermal necrolysis

Disease
Staphylococcal scalded skin syndrome
Other severe adverse drug reactions:
Acute generalized exanthematous pustulosis
DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms)
Drug-induced linear IgA dermatosis
Erythema multiforme
Lupus erythematosus with symptoms similar to TEN
Acute graft versus host disease (GVHD)
Paraneoplastic pemphigus
Kawasaki disease (in children)
Thermal and chemical burns

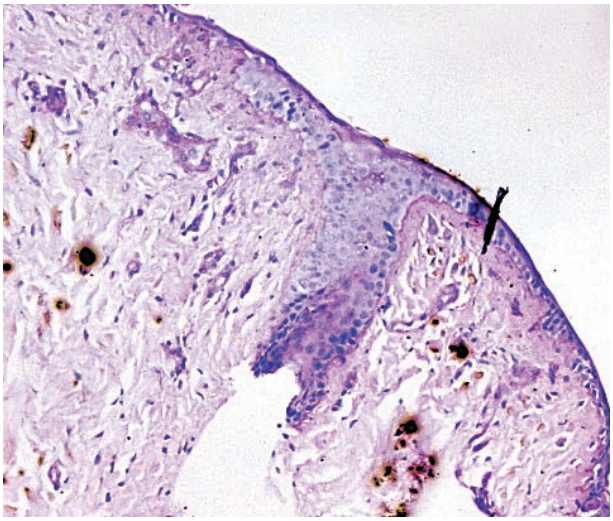

Figure 4. Subepidermal cleavage with confluent keratinocyte necrosis of the whole epidermis and sparse perivascular lymphocytic infiltrate in the dermis (H&E x100)

keratinocytes in the histopathological biopsy finding, it is possible to confirm the clinical diagnosis and make a differential diagnosis in relation to other diseases with symptoms of epidermal detachment (Table 3.).

Course and prognosis

Re-epithelialization starts 2-3 days after the onset of TEN, even concomitantly with emergence of new lesions, and it ends after 2-3 weeks. Long-term follow-up data on patients with TEN are scarse. The most common long-term morbidity involves the eyes, which means that consultation with ophthalmologist is mandatory in these patients, as well as intensive topical ophthalmologic therapy. During acute phase of the disease, ocular sequelae include development of entropion, symblepharon and synechiae, as well as dry eye, even in patients without significant eye mucous membrane involvement (1-5, 22). Sequelae also include nail dyschromia, whereas cutaneous scarring rarely leads to disturbances in affected persons. Management of oral mucous membrane and tongue lesions has been reported, as well as of genital (vaginal) mucous membranes, which may cause synechiae. That is why local intensive care of both oral and genital mucous membranes is of great importance.

The treatment outcome depends on several factors, while older age, multiple drug use, late exclusion of the drug inducing TEN, raised serum levels of urea, creatinine and cytopenia are poor prognostic indicators (22). Bastuji-Garin and associates created a scoring system called SCORTEN, which proved to be of great help in the assessment of disease outcome, although based on SCORTEN, some authors found an overestimated risk for lethal outcome in their patients (23-25) (Table 4.).

Treatment approaches

The basic approach to the treatment of toxic epidermal necrolysis is recognition of the disease, immediate

Table 4. SCORTEN – a TEN-specific severity of illness and mortality score

Clinical-biological parameters	Individual score	SCORTEN	Expected mortality (%)
Age > 40 years	Yes – 1, No - 0		
Malignant disease	Yes – 1, No - 0	0 - 1	3.2
Tachycardia > 120/min	Yes – 1, No - 0	2	12.1
Initial epidermal involvement >10%	Yes – 1, No - 0	3	35.3
Serum urea >10mmol/L	Yes – 1, No - 0	4	58.3
Serum glucose > 14mmol/L	Yes – 1, No - 0	>5	90
Bicarbonates < 20mmol/L	Yes – 1, No - 0		

suspension of the probable inducing drug, and emergency transport to the closest burn center. It was found that the treatment in burn units is associated with a lower risk of infection and mortality of these patients, as well as shorter hospital stay (26 – 28).

General measures

General measures are fundamental for the outcome of the disease, including metabolic balance control and skin care, which is essential for prevention of skin infections and sepsis.

Anamnestic data should provide information on a new drug introduced during the past month, and even earlier appearance of skin reactions associated with certain medications. It is necessary to exclude from therapy all unnecessary medications and any medication that is suspected to cause TEN (1-5, 26, 28). Initial lab tests should include sedimentation rate (ESR), C-reactive protein (CRP), complete blood count (CBC) with leukocyte formula, biochemical tests including urea, creatinine, albumins, total proteins, total bilirubin, electrolytes, liver enzymes, biochemical analysis and analysis of urinary sediment, procalcitonin if DRESS syndrome is suspected, and IgA if intravenous immunoglobulin therapy is intended. Also, chest x-ray is recommended. In case of fever it is necessary to obtain blood, urine and sputum cultures, as well as eye and skin swabs on admission, and later every three days. Skin biopsy is necessary for histopathological analysis and direct immunofluorescence, best obtained on the borderline of the affected and nonaffected skin (1-5, 26, 28).

In order to prevent hypothermia, the room temperature should be maintained at 30º C. Based on laboratory findings, fluid and electrolyte replacement is initiated, preferably using peripheral venous access, which is better than using a central venous catheter (28). Fluid replacement requirement is lower than in patients with burns, so monitoring and maintenance of diuresis is mandatory at 60-80 ml/h, in order to avoid hypervolemia. Broad spectrum antibiotics are not recommended if there are no signs of sepsis or infection, but if they are present, the therapy should be modified according to the antibiogram results based on microbiological analyses. If there is doubt, serological test for *Mycoplasma pneumoniae* should be performed, which is recommended as routine analysis in TEN patients, in some centers (1-5, 28).

If food intake is not possible, it is best to start with total parenteral nutrition (TPN), because it is associated with better disease outcome (29). Except for oral cavity erosions, gastrointestinal mucous membrane involvement significantly reduces absorption of nutrients, so in this case TPN is more effective (1-5). Just as in patients with burns, nutritional requirements are calculated according to the percentage of the affected area (29). On the other hand, some centers use nasogastric tubes for nutrition, while other authors point out that due to involvement of the gastrointestinal tract, it should be avoided, and the decision should be made individually for each patient (1-5, 29). As in intensive care patients, prevention of deep vein thrombosis is necessary using low molecular heparin, as well as prevention of stress ulcerations using proton pump inhibitors. In case of significant leukopenia development (1000/ml), use of G-CSF (filgrastim) growth factor is indicated (1-5, 28). Consultations with ophthalmologists, otolaryngologists, gastro-enterologists and pulmologists are necessary for evaluation of certain mucous membrane involvement, as well as for choosing adequate therapy. That is why a multidisciplinary approach to treatment is of great importance for a favorable outcome.

Local therapy and skin care

Today, conservative wound treatment is essential. Bullae should be punctured, and roof should be left on the skin, since it can speed re-epithelialization. Debridement is done only in areas with pronounced necrosis and if signs of infection are present. A non-adhesive vaseline-impregnated dressing is a good choice at places where the epidermis is present, whereas according to different studies, open erosions should be treated by special silver-impregnated dressings, artificial skin substitutes, or biological materials which are not easy to obtain (1-5, 28). According to the protocols, published by the University of Miami in 1991 and 2007, including guidelines for TEN therapy, non-adhesive dressings with 0.5% silver-nitrate changed every three days are sufficient for infection control, which can significantly facilitates patient care (28). A group of authors, however, believe that preparations containing silver sulfadiazine may be used in patients without hypersensitivity to medications with sulfa group, whereas Guidelines of the University of Miami

do not recommend silver-sulfadiazine in patients with TEN, especially not on large body surfaces, due to risk of systemic sesnsibilization and leukopenia (28).

Management of mucous membranes and early inclusion of ophthalmologists in the treatment is necessary to prevent complications, especially development of synechiae. Vaseline impregnated gauze is used for the lips, oral antiseptics are used for mouth wash (hydrogen peroxide, chlorhexidine and so on) and anesthetics in oral gel for reduction of oral pain. Ophthalmologic treatment includes administration of eye drops every 2-3 hours, and combination of antibiotics and corticosteroid creams preparations every 6 hours. Vaseline dressing in the genital area is recommended few times a day, and are also very important for prevention of synechiae (1-5, 28).

Pharmacological therapy

Exclusion of the drug inducing TEN, and supportive therapy, is the first and only therapy for which there is a consensus in different centers. Various forms of adjuvant therapy are applied in various countries. In France, supportive therapy is a standard of care, in Germany it is short-term use of high-dose corticosteroids, while in USA, in the last decade high-dose intravenous immunoglobulins are the most widely accepted treatment modality (1-5, 26, 28). A retrospective multicetner European study (EuroSCAR), published in January of 2008, including 75 patients, showed that there is no certain evidence that treatment with intravenous immunoglobulins and short-term corticosteroid pulse therapy have any effects on TEN outcomes. Similar studies examined effects of plasmapheresis, cyclosporine and other immunosuppressants (30).

In some studies, use of corticosteroids showed positive effects on disease outcome, while in other increased mortality was reported. That is why majority of experts today believe that long-term use of corticosteroids is contraindicated in patients with TEN, due to prolonged re-epithelialization and increased risk of sepsis. Also, in the presence of TNF-α, corticosteroids decrease NF-KB expression and proapoptotic effects, possibly explaining poor disease outcome with use of corticosteroids (26, 31). In some centers, primarily in Germany, the use of corticosteroids continued in the form of pulse therapy of 250 mg during 2-5 days (30, 32). However, the multicenter study from 2008, EuroSCAR, showed that the average 5-day 60 mg corticosteroid therapy (in France) and 250 mg a day (in Germany) did not affect disease outcome, but authors suggest that their effects could probably be shown in a larger study. Until then, use of high-dose corticosteroid therapy may be justified only in the early phase of the disease, while long-term therapy is contraindicated (1-5, 26, 31).

High-dose intravenous immunoglobulin therapy has been accepted by some experts in USA as the first line therapy in the last decade based on findings that intravenous immunoglobulins can inhibit Fas-FasL interaction. Most studies investigating intravenous immunoglobulin therapy – 3-4 g/kg/BW (1g/kg/BW a day, during 3 days) in the first 48-72 hours from the onset of the disease, showed relief of symptoms and fast re-epithelialization, as well as significantly lower mortality in comparison to historic controls in one study, and in comparison to supportive measures in another (33, 34). In several studies, however, intravenous immunoglobulins showed no significant difference in disease outcome, although in many of them the dosage of immunoglobulins was lower, or the therapy was initiated after 48-72 hours from the onset (30, 35). EuroSCAR study from 2008, conducted in several European countries, reported no significant effects of intravenous immunoglobulin therapy, but the average dose used in patients was only 1.9g/kg/BW (35).

Plasmapheresis has proven successful in treating various antibody and immune complex mediated diseases. Several studies have shown favorable effects of plasmapheresis on the course of TEN, whereas in some studies it was combined with primary intravenous immunoglobulins with accelerated effects (36, 37, 38). It is not known whether the effect of plasmapheresis is associated with removing the drug inducing the disease from the blood, or removing the inflammatory mediators. However, in two case reports, patients treated with plasmapheresis showed decreased concentrations of Il-6, IL-8, and TNF-alpha in 1 patient, which may explain the mechanism of action of this treatment modality (39).

A total of 18 patients with TEN, reported so far, was treated with cyclosporine, due to the role of T-lymphocytes in the pathogenesis of the disease, with favorable effects on promoting re-epithelialization, but it was a small sample and an uncontroled study

(38-40). Nonetheless, Arevalo and associates treated 11 patients with cyclosporine (3mg/kg/BW) and reported reduced mortality in regard to the control group of patients with the same anamnesis who were not treated with cyclosporine (40). Prospective studies are necessary for the final verdict on this modality of treatment. Furthermore, due to the importance of TNF-alpha in the pathogenesis of the disease, biological therapy with infliximab and etanercept was used in individual cases with TEN, with fairly good response to therapy (41, 42).

Cyclophosphamide was also used in individual cases, but given its significant side effects and lack of evidence of its effectiveness, this medication is not recommended in the current treatment of TEN (2). Wolkenstein and associates started a placebo-controlled study of thalidomide with immunosuppressive and anti-angiogenic effects, mediated by reduced release of TNF-alpha from monocytes. However, the study was ended because higher mortality was recorded in the group of patients receiving thalidomide (43).

Conclusion

In conclusion, toxic epidermal necrolysis is one of the most serious emergency conditions in dermatology. Elimination of the possible causal agent, rapid transport to the burn unit, and multidisciplinary approach to treatment are of utmost importance for favorable outcome of the disease with mortality rate reduced to 20-30%.

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Novine u dijagnostici i lečenju toksične epidermalne nekrolize

Sažetak

Definicija: Toksična epidermalna nekroliza (TEN) je idiosinkratička reakcija na lek, koju je, usled masivne nekroze keratinocita, karakteristična po ekstenzivnom odvajanju epiderma i zahvatanjem sluzokoža sa potencijalnim smrtnim ishodom zbog mogućih komplikacija.
Istorijski podaci: Oboljenje slično toksičkoj nekrolizi epiderma prvi put je opisao Ruskin 1948. godine, dok je škotski dermatolog Alan Lajel (Alan Lyell) 1956. objavio četiri slučaja akutnog egzantema sa zahvatanjem sluzokoža, po kome je ovo oboljenje dobilo svoj drugi naziv – Lajelova bolest. Lajel je u nazivu bolesti kombinovao epidermolizu kao glavnu kliničku i nekrozu kao glavnu histopatološku odliku bolesti. Dva pacijenta, od opisanih četiri, zapravo su bili oboleli od stafilokoknog sindroma oparene kože (engl. *staphylococcal scalded skin syndrome*, SSSS), te je autor smatrao je oboljenje izazvano i posredovano bakterijskim toksinima, nazivajući je *toksičkom*. I danas, uprkos tome što je dijagnoza TEN najčešće klinička, biopsija kože sa histopatološkom analizom ima značajnu ulogu u diferencijalnoj dijagnozi ova dva oboljenja, posebno u pedijatrijskoj populaciji.
Etiopatogeneza: Imajući u vidu da je idiosinkratička, može se javiti potpuno nepredvidivo i nezavisno od

primenjene doze leka, od 7. do 21. dana od započinjanja terapije, i to najčešće izazvana sledećim lekovima: sulfonamidi, alopurinol, karbamazepin, fenobarbiton, fenitoin i oksikamski nesteroidni antiinflamatorni lekovi. Imajući u vidu da je u pitanju idiosinkratička reakcija na lek, ona može da se javi kod bilo koga, ali je verovatno da postoji genetska predispozicija, kao što je slučaj sa većom učestalošću HLA B12 kod pacijenata sa TEN, HLA*B5801 kod pacijenata sa SJS/TEN reakcijom na alopurinol i HLA*B1502 kod pacijenata koji su imali reakciju na karbamazepin u različitim populacijama. Povećan rizik od nastanka TEN zabeležen je kod osoba sporih acetilatora, kod imunokompromitovanih (HIV infekcija i limfomi) i kod osoba sa tumorima mozga koji su na radioterapiji i uzimaju antikonvulzive.

Period od jedne do 3 nedelje, koji prođe od početka uzimanja leka do razvoja reakcije TEN, ukazuje na to da je specifičan imunoodgovor odgovoran za nastanak oboljenja. Kod osoba koji su već imale manifestacije SJS/TEN, ovaj period je znatno kraći. Patogenetski supstrat toksičke epidermalne nekroliza je masivna apoptoza keratinocita izazvana lekom, aktivicijom indukovane apoptoze posredovane $CD8^+$ citotoksičnim limfocitima specifičnim za lek (a ne za njegove metabolite, kako se ranije pretpostavljalo). Postojanje citotoksičnih CD8+ limfocita specifičnih za lek je pokazano u dve studije. Prisustvo CD8+ T-limfocita koji eksprimiraju i kutani limfocitni antigen (engl. *cutaneous lymphocyte antigen-CLA*), koji je odgovoran za usmeravanje T-limfocita u kožu, evidentno je već u ranim fazama TEN. Dokazano je da je citotoksičnost T-ćelija u TEN posredovanoj grenzimom koji izaziva programiranu ćelijsku smrt aktivacijom prokaspaze-8 i perforinom koji dovodi do stvaranja pora na ćeliji koja je u kontaktu sa T-limfocitom. U lezijama TEN zabeležena je povećana ekspresija IL-6, TNF-α, IL-18, interferona-γ i FasL, poreklom od T-limfocita, monocita/makrofaga i keratinocita. Prisustvo navedenih citokina odgovorno je za opšte simptome koji prate oboljenje, dok je povećana ekspresija FasL na površini keratinocita, najverovatnije indukovana interferonom γ odgovorna za masovnu apoptozu keratinocita interakcijom sa Fas molekulom, koji se konstitutivno eksprimira na površini keratinocita. Osim ekspresije FasL na keratinocitima, zabeleženo je prisustvo solubilnog FasL u serumu pacijenata sa TEN i pokazana njegova sposobnost da indukuju apoptozu normalnih keratinocita. Povećana koncentracija IL-10 koja je takođe utvrđena, verovanto ima ulogu u terminaciji imunoreakcije.

Dijagnoza, diferencijalna dijagnoza oboljenja i procena težine bolesti: Dijagnoza bolesti postavlja se pre svega na osnovu tipične kliničke slike, ali je neophodno učiniti biopsiju kože radi histopatološke analize i direktnog imunofluorescentnog pregleda.

Histopatološka analiza ukazuje na prisustvo subepidermalnog rascepa sa konfluentnom nekrozom keratinocita celog epiderma i blago izraženim perivaskularnim limfocitnim infiltratom u dermu. Brza histopatološka dijagnoza moguća je i na osnovu pregleda kriostatskih preseka kože. Imunohistohemijski, limfociti koji su prisutni u epidermu su $CD8^+$, dok su oni u papilarnom dermu pripadaju $CD4^+$ subpopulaciji. Direktni imunofluorescentni pregled je važan za diferencijalnu dijagnozu TEN i autoimunih buloznih dermatoza od kojih su neke takođe pokrenute lekom, kao i eritemskog lupusa. Na osnovu kliničke slike i nalaza masovne nekroze keratinocita u histopatološkom nalazu bioptata kože, moguće je potvrditi kliničku dijagnozu i napraviti diferencijalnu dijagnozu u odnosu na druga oboljenja koja se manifestuju odvajanjem epiderma.

Lečenje: Osnovni pristup lečenju je što ranija obustava leka uzročnika i svih nepotrebnih lekova u terapiji, te hitan transport u jedinicu za opekotine, jer je lečenje u njoj povezano sa nižim rizikom od infekcije i smanjenjem smrtnosti ovih bolesnika. Postignut je konsenzus u različitim centrima u svetu da terapiju izbora predstavljaju prekid terapije inkriminisanim lekom i simptomatska potporna terapija: nadoknada tečnosti i elektrolita, regulacija temperature, parenteralna ishrana, lokalna terapija i nega kože i sluzokoža. Različiti oblici adjuvantne terapija primjenjuju se u različitim zemljama: u Francuskoj, suportivna terapija je standard lečenja, u Nemačkoj to je kratkotrajna primena visokih doza korstikosteroida (2-5 dana), dok je u SAD-u, u poslednjih deset godina terapija visokim dozama intravenskih imunoglobulina široko prihvaćen način lečenja. Prikazi slučajeva i prikazi serija ispitivanja koji su sprovedeni na malom broju pacijenata opisuju i povoljan terapijski učinak plazmafereze, ciklosporina i drugih imunosuppresiva.

Lokalna terapija i nega kože: Danas preovlađuje stav o konzervativnoj obradi rana: bule je potrebno probušiti i epiderm ostaviti kao prirodnu oblogu koja će ubrzati epitelizaciju, dok je debridman potreban samo na pojedinim mestima sa izraženom nekrozom i znacima

infekcije. Sloj neadhezivnih zavoja impregniranih vazelinom na mestima gde je epiderm prisutan je dobar izbor, dok na mestima gde postoje otvorene erozije, u različitim studijama su opisani ili posebne obloge impregnirane najčešće srebrom, veštački supstituenti kože, ili biološki materijali koji su teško dostupni. Prema protokolima sa Univerziteta u Majamiju koji su u 1991. i 2007. godine objavili svoje vodiče za lečenje TEN, neadhezivni oblozi sa 0,5% srebro-nitratom su dovoljni za kontrolu infekcije, a menjaju se na svaka tri dana, što značajno olakšava negu. Prema jednim autorima, preparati sa srebrosulfadijazinom mogu da se primenjuju kod pacijenata koji nisu preoseltjivi na lekove sa sulfa grupom, dok je prema vodiču sa Univerzieta u Majamiju srebrosulfadijazin ne treba primenjivati kod pacijenata sa TEN, posebno ne na velike površine tela, zbog rizika od sistemske senzibilizacije i leukopenije.

Nega sluzokoža i rano uključivanje oftalmologa u lečenje je neophodno za sprečavanje komplikacija tokom ožiljavanja, pre svega stvaranja sinehija. Gaze impregnirane vazelinom za usne, ispiranje usne duplje oralnim antiseptikom (vodonik-peroksid, hlorheksidin, i sl.), primena lokalnog anestetika u vidu gela za usnu duplju sa ciljem smanjenja bolova u usnoj duplji osnova su simptomatske terapije oralne sluzokože. Oftalmološka terapija podrazumeva primenu veštačkih suza na svaka 2-3 sata, kombinaciju antibiotika i kortikosteroida u vidu oftalmološke masti svakih 6 sati. Primena vazelina za regiju genitalne sluzokože više puta dnevno je takođe važna za sprečavanje stvaranja sinehija.

Farmakološka terapija: Isključivanje leka uzročnika TEN iz terapije i suportivna terapija su prva i jedina terapija za koju postoji konsenzus među različitim centrima. Stav većine autora danas jeste da je dugotrajna primena kortikosteroida kod pacijenata sa TEN kontraindikovana, zbog mogućeg produženja vremena reepitelizacije, i povećanja rizika od sepse. U nekim centrima, pre svega u Nemačkoj, primena kortikosteroida je nastavljena u vidu kratkotrajnih pulseva od 250 mg tokom tokom 2-5 dana. Primena kortikosteroida je možda opravdana samo u ranoj fazi bolesti u visokim dozama, dok je dugotrajna terapija kontraindikovana.

Terapija visokim dozama intravenskih imunoglobulina prihvaćena je u poslednjoj deceniji na osnovu nalaza moguće blokade Fas-FasL interakcije primenom ove terapije. U većini studija sa primenom IvIg u dozama od 3-4 g/kg TT (1g/kg TT dnevno, tri dana) i to u prvih 48-72 h od početka bolesti, pokazano je zaustavljanje širenja promena i brza epitelizacija. U nekoliko studija, međutim, nije pokazan značajan efekat intravenskih imunoglobulina, mada je u mnogima od njih doza primenjenih imunoglobulina bila manja ili je početak terapije bio posle 48-72 h. Plazmafereza se pokazala uspešnom u lečenju različitih oboljenja posredovanih antitelima i imunokompleksima. U TEN, u nekoliko studija je pokazan povoljan efekat plazmafereze na tok bolesti, a u nekima je plazmafereza bila kombinovana sa primenom intravenskih imunoglobulina sa brzim efektom. Nije poznato da li je efekat plazmafereze povezan sa uklanjanjem leka – uzročnika iz krvi ili uklanjanjem inflamatornih medijatora, mada je u prikazu slučaja dva pacijenta lečena plazmaferezom zabeleženo smanjenje koncentracije IL-6, IL-8 i TNF-α kod jednog pacijenta, što može da objasni mehanizam dejstva ovog modaliteta terapije.

Biološka terapija infliksimabom i etanerceptom korišćena je u pojedinačnim slučajevima TEN sa dobrim odgovorom na terapiju.

Ciklofosfamid nema mesto u savremenoj terapiji. Wolkenstein i saradnici su započeli placebom kontrolisanu studiju primene talidomida, koji ima imunosupresivne i antiangiogene efekte, posredovane između ostalog smanjenjem oslobađanja TNF-α iz monocita. Ipak, studija je prekinuta jer je zabeležen veći mortalitet u grupi kod koje je primenjen talidomid.

Tok i prognoza: Loši prognostički faktori kao što je starije životno doba, primena multiplih lekova, kasno isključenje leka – uzročnika, pojava uremije, povišenih vrednosti kreatinina i citopenije, zbirno se boduju u SCORTEN sistemu, koji se pokazao korisnim u proceni ishoda bolesti čija je smrtnost 20-30%.

Zaključak: Prekid terapije lekom verovatnim uzročnikom, hitan transport u jedinicu za opekotine i multidisciplinarni pristup lečenju su najvažniji za povoljan ishod bolesti.

Ključne reči

Toksična epidermalna nekroliza + dijagnoza + terapija + etiologija + epidemiologija; Toksičnost lekova; Znaci i simptomi; Tok bolesti; Mortalitet; Prognoza