Microbiological findings and antimicrobial resistance dynamics in pathogens isolated from patients with toxic epidermal necrolysis: a single center experience

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ABSTRACT

Introduction: Toxic epidermal necrolysis (TEN) is one of the most life-threatening skin exfoliative disorders. The disease is frequently misdiagnosed or diagnosed with a long delay. This, together with the unique pathology, leads to a high mortality of affected patients. The high risk of infections associated with extensive loss of skin and impaired function of the immune system is one of the most common complications in TEN patients.

Methods: All patients treated at our clinic with a diagnosis of TEN between January 1, 1996, and December 31, 2020, were included in this study. Basic epidemiological parameters, the incidence of infectious complications in individual compartments, clinical laboratory and microbiological parameters, and antimicrobial resistance of pathogens isolated during the hospital stay were collected.

Results: In total, 498 potentially pathogenic microorganisms (PPMs) were isolated in our patient group, i.e., on average more than 35 isolated PPMs per patient. Of these, 155 pathogens fell into the gram-positive spectrum (31.1%), and 331 into the gram-negative spectrum (66.5%). The effect of corticosteroid therapy on overall survival is also an interesting indicator. In patients with multifocal infection, the maximum corticosteroid dose was 965 mg of methylprednisolone, while in patients without multifocal infection, the maximum dose was 2.333 mg methylprednisolone ($p = 0.032$). Last but not least, we mapped the most frequently occurring pathogens, dominated by gram-negative bacteria, in particular *Klebsiella* sp. and *Enterobacter* sp. We also described the presence of antibiotic resistance in epidemiologically important pathogens in TEN patients with infectious complications.

Conclusion: We successfully identified basic epidemiological parameters in a cohort of patients treated with TEN along with the most frequent representatives of infectious complications. We were able to identify risk factors for the development of infectious complications and their impact on further complications of treatment as well as patient mortality.

KEYWORDS

toxic epidermal necrolysis – infectious complications – antimicrobial resistance

SOUHRN

Holoubek J., Matysková D., Hanslianová M., Cvanová M., Lipový B.: Mikrobiologické nálezy a dynamika antimikrobiální rezistence u patogenů izolovaných od pacientů s toxickou epidermální nekrolýzou: zkušenosti z jednoho centra

Úvod: Toxická epidermální nekrolýza (TEN) představuje jedno z nejzávažnějších exfoliativních onemocnění kůže s vysokou mortalitou. Onemocnění bývá často chybně diagnostikováno nebo diagnostikováno s výrazným časovým odstupem, což v kombinaci s jeho specifickou patogenezí významně přispívá k nepříznivé prognóze pacientů. Jednou z nejčastějších a nejzávažnějších komplikací u pacientů s TEN je vznik infekcí, které souvisejí s rozsáhlou ztrátou kožní bariéry a dysfunkcí imunitního systému.

Metodika: Do retrospektivní studie byli zařazeni všichni pacienti léčení na našem pracovišti s diagnózou TEN v období od 1. ledna 1996 do 31. prosince 2020. Byly analyzovány základní epidemiologické charakteristiky souboru, incidence infekčních komplikací v jednotlivých anatomických lokalizacích, klinicko-laboratorní a mikrobiologické ukazatele a dále antimikrobiální rezistence patogenů izolovaných v průběhu hospitalizace.

Výsledky: V souboru bylo celkem identifikováno 498 potenciálně patogenních mikroorganismů (PPM), tj. průměrně více než 35 izolátů na jednoho pacienta. Z tohoto počtu představovalo 155 izolátů (31,1 %) grampozitivní bakterie a 331 izolátů (66,5 %) bakterie gramnegativní. Zajímavým zjištěním byl vztah mezi podáváním kortikosteroidní terapie a celkovým přežitím. U pacientů s multifokální infekcí činila maximální dávka methylprednisolonu 965 mg, zatímco u pacientů bez multifokální infekce 2 333 mg ($p = 0,032$). Dále byla zmapována nejčastější etiologie infekčních komplikací, jimž dominovaly gramnegativní bakterie, zejména

rody *Klebsiella* a *Enterobacter*. Popsána byla rovněž přítomnost antimikrobiální rezistence u epidemiologicky významných patogenů izolovaných u pacientů s TEN s infekčními komplikacemi.
Závěr: Studie identifikovala základní epidemiologické charakteristiky souboru pacientů léčených pro TEN, nejčastější původce infekčních komplikací a faktory rizika pro jejich vznik. Bylo doloženo, že tyto infekční komplikace významně ovlivňují průběh onemocnění, léčebnou strategii i mortalitu pacientů.

KLÍČOVÁ SLOVA
toxická epidermální nekrolýza – infekční komplikace – antimikrobiální rezistence

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INTRODUCTION

Toxic epidermal necrolysis (TEN), also known as Lyell's syndrome, is one of the most severe skin diseases. It belongs to the group of SCARs (severe cutaneous adverse reactions) [1]. The etiology of the disease is very diverse. The list of drugs causing the disability includes hundreds of items [2].

The essence of TEN lies in the induction of apoptosis in the dermo-epidermal junction, which leads to the initiation of a widespread exfoliative process. Moreover, necroptosis has been proposed as another potential mechanism [3]. The extent of skin involvement (exceeding 30% of TBSA) is a key point in differentiating TEN from other SCAR diseases. A prompt and correct diagnosis, which relies primarily on the clinical picture and histological verification, is crucial for the successful treatment of TEN [4].

Since its discovery, a variety of theories and considerations on TEN pathophysiology have been developed. The data published so far show that at least 3 pathophysiological pathways are behind the development of this disease. The first is the interaction between Fas-R (CD95R) and Fas-L (CD95L) keratinocytes (lymphocytes), which triggers apoptosis through effective caspase 8. In the second pathophysiological pathway, TNFα plays an important role. The third pathway is the direct action of CD8+ and CD4+ lymphocytes with NK cells on the keratinocyte cell wall via granzyme B, perforin and granulysin. The result is a disruption of keratinocyte homeostasis and apoptosis [5].

It is not surprising that patients affected in this way are exposed to numerous infectious complications due to compromising the immune system. This is not only due to the loss of skin cover as a primary barrier against infection, but also due to the strong immunosuppressant therapy, which is the cornerstone of treatment [6]. The aim of this paper is to summarize our experience with infectious complications in patients with TEN. We were able to identify the most common pathogens according to the individual infectious sites. Finally, we desribed the individual antibiotic resistance of these pathogens.

METHODS

Basic epidemiological characteristics of the patient population

All patients with a diagnosis of TEN treated at our clinic between January 1, 1996, and December 31, 2020, were enrolled in this study. Basic epidemiological parameters (age and sex) along with clinical parameters, such as the duration of hospitalization, the presence of mucosal involvement, the extent of skin exfoliation, the need for mechanical ventilation and its duration, and the need for tracheostomy were collected. In addition, TEN severity was assessed using two dedicated scoring systems: the Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN) [7], and the Algorithm for Assessment of Drug Causality in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (ALDEN) [8]. Clinical laboratory parameters (biochemical, microbiological, and hematological) were also recorded. Particular attention was paid to infectious complications and their causative agents, as these are nowadays the dominant contributors to the mortality of TEN patients.

Microbiological testing and analysis

In all patients, swabbing of exfoliated surfaces was performed with a sterile cotton swab dipped in the transport medium (AMIES). After the transport to the microbiology laboratory, the material was plated on culture media – blood agar, McConkey agar (selective agar for gram-negative microbes), blood agar with added NaCl (selective agar for staphylococci), and Wilkins-Chalgren (VL) agar (culture of anaerobic microbes). The swabbing advantage is the possibility of anaerobic cultivation and identification of anaerobic pathogens.

Imprints from exfoliated surfaces were made by attaching strips of sterile filter paper on the exfoliated area and transfered to culture media – blood agar, McConkey agar, URIselect (chromogenic culture medium for the capture of gram-negative and gram-positive microbes with color differentiation of growth). This quantitative method allows quantitative monitoring of the microbial colonization of the exfoliated

area, its changes over time, and, thus, the efficacy of treatment. With this method, growing bacterial colonies are counted. 10^1 amount of colonies is more likely colonization, 10^2 and more amout of colonies give evidence for infection. The disadvantage is lack of anaerobic cultivation.

Blood agars as well as blood agars with addes NaCl were cultivated 18–24 hours in atmosphere with increased CO_2 level, McConkey agars and URI select plates were cultivated 18–24 hours in standard atmosphere and cultivation of VL agars were 48 hours in anaerobic atmosphere. Cultivation temperature was 37 °C.

All agars are examinated after given time of cultivation, grown colonies visible on the agars are indeficated mostly using mass spectrometry (MALDI-TOF, Bruker). According to type of microbes, in some cases biochemical identifications using API tests were performed.

Biological material from the respiratory tract was applied to the basic culture media – blood agar and McConkey agar. Materials collected from the lower respiratory tract were further inoculated on VL agar for anaerobic processing. For liquid samples (broncho-alveolar lavage), blood agar was substitude with added NaCl and chocolate agar (enriched with nutrients derived from erythrocyte lysis for better growth of more demanding microbes, such as the *Haemophilus* sp.). Chocolate agar was cultivated 18–24 hours in atmosphere with increased CO_2 level, 37 °C temperature, other agars as listed above.

Hemoculture was processed as follows*:* a defined amount of blood collected from the patients was immediately transferred into aerobic and anaerobic hemoculture vials with a specific medium. Vials were cultivated using the blood culture system Bactec Becton Dickonson (New Jersey, USA). In case of a positive result caused by growing microorganisms, the vials were removed from the device and their content was applied to the culture media – blood agar, McConkey agar, and URIselect. In the case of an anaerobic cultivation, the material was inoculated on VL agar for anaerobic cultivation. If necessary and indicated, slides for microscopy were also prepared.

Urine samples were delivered to the laboratory within two hours after their collection. The sample was applied to blood agar, McConkey agar, and URIselect. All samples were processed and evaluated by experienced microbiologists at the Department of Microbiology, University Hospital Brno, Czech Republic.

Throughout the entire monitoring period, the methodology for microbial identification evolved. Until 2011, biochemical methods were predominantly used. However, since then, mass spectrometry (MALDI-TOF – Matrix-Assisted Laser Desorption/Ionization Time-of-Flight) has been employed exclusively. Another modification involved the addition of URI select agar to the culture media used for wound surface swabs and imprints.

Statistic analysis

Continuous variables are described by the mean, median, minimum, and maximum. Results are reported as mean ± standard deviation. Categorical variables are described as the numbers of persons and percentages. Non-parametric tests were used for statistical evaluation due to the assumption of non-normality of the data and due to the small number of patients in the cohort. The results of the statistical evaluation are described as p-values of the Mann-Whitney test for the comparison of the probability distributions of continuous and ordinal variables between the two groups of patients. The independence of the two categorical variables was assessed by Fisher's exact test. The bolded p-values are statistically significant at the 0.050 level of significance (p-value ≤ 0.050). At the point in time when there is only one patient in one of the assessed groups or categories, the statistical evaluation is not performed and the p-value is replaced by '-'.

RESULTS

Basic epidemiological data

In total, 14 patients with the diagnosis of TEN were included. Of that number, only 3 were men (M : F ratio of 1 : 3.7). The mean age of the patients in the cohort was 50.0 ± 23.8 years, the mean range of exfoliated area was 69.4 ± 25.7% of TBSA. All patients in the cohort were transferred to our department secondary to a primary hospitalization for TEN or other diseases the treatment of which led to the development of TEN. The severity of the overall condition was assessed using SCORTEN (SCORe of Toxic Epidermal Necrosis). The mean value of this index for all patients in the cohort was 3.4 ± 1.1, with two patients achieving 5, representing up to 90% prediction of mortality. The mean SCORTEN value was 3.6 ± 1.0 in patients who died and 3.1 ± 1.2 for survivors. The mean time between the onset of symptoms and the admission to our department was 5.6 ± 2.3 days for patients who died and 8.3 ± 5.6 days for those who survived. The mean length of hospitalization was 23.5 ± 14.0 days for all patients; deaths occurred after 14.3 ± 13.4 days of hospitalization. A total of 11 patients (78.6%) required mechanical ventilation (MV) during hospitalization. The mean duration of MV in all patients, which required MV, in the cohort was 10.5 ± 7.6 days; in deceased patients. It was 8.4 ± 5.0 days. Histological confirmation of diagnosis was performed in 7 patients (all of them were hospitalized after 2007). Before that year, histological confirmation was not performed at our department. Three surviving patients suffered a loss of ability to re-epithelialize a part of the exfoliated areas, with the only possibility of definitive closure represented by dermo-epidermal grafting. Only in one patient with skin defect wounds progressed into full thickness defect, which required

autotransplantation with a split-thickness skin grafts (STSGs), the remaining patients died due to the progression of an underlying disease. Due to the relatively small number of patients in our cohort, it is not possible to unequivocally identify a single risk agent for the development of TEN. The most frequently identified groups of drugs were anticonvulsants (lamotrigine, valproate, phenytoin) or antimicrobials (aminopenicillins, trimethoprim-sulfamethoxazole). Background epidemiological indicators together with other relevant data are summarized in table 1. The mortality in our cohort reached 50% (7/14). No statistically significant risk factor for predicting mortality was detected among the studied basic epidemiological indicators. Table 2 describes the most important epidemiological and laboratory parameters monitored in the context of mortality.

Infectious complications, spectrum of potentially pathogenic microorganisms, and risk factors for the development of infection in patients with TEN

Infectious complications occurred during hospitalization in all patients in the cohort. Multifocal infections, i.e. infectious complications diagnosed in two or more compartments, were recorded in 11 patients (78.6%).

The effect of the amount of administered corticosteroids on the development of infectious complications

In total, 8 patients in the cohort were administered less than 1000 mg of methylprednisolone (hereinafter designated as "low-dose") daily and six patients received more than 1000 mg/day ("high-dose"). All 8 low-dose patients were diagnosed with multifocal infection, while only half of high-dose patients (i.e., three) developed multifocal infections. The maximum corticosteroid doses were 965 mg and 2333 mg of methylprednisolone in patients with and without multifocal infection, respectively ($p = 0.032$). Thus, lower doses of corticosteroids are more effective in terms of the development of multifocal infection, even at the level of statistical significance. Another data point is a statistically significant difference related to infectious complications caused by gram-negative bacteria within 48 hours of the start of hospitalization. The infection

Table 1. Basic epidemiological parameters of the patients

		Exitus			0-7 days mortality		8-28 days mortality		29-50 days mortality		Statistical analysis			
		Total	Yes	No	Yes	No	Yes	No	Yes	No	Exitus	0–7 days mortality	8–28 days mortality	29–50 days mortality
N		14	7	7	2	12	4	8	1	7	p-value	p-value	p-value	p-value
Age		50; 50 (20; 81)	53; 68 (20; 77)	47; 31 (20; 81)	48; 48 (20; 75)	50; 50 (20; 81)	52; 51 (30; 77)	50; 49 (20; 81)	68; 68 (68; 68)	47; 31 (20; 81)	0.701	0.647	0.609	–
Sex	Male	3 (21%)	2 (29%)	1 (14%)	1 (50%)	2 (17%)	0	2 (25%)	1 (100%)	1 (14%)				
	Female	11 (79%)	5 (71%)	6 (86%)	1 (50%)	10 (83%)	4 (100%)	6 (75%)	0	6 (86%)				
Time from first signs to admission (days)		8; 6 (2; 16)	6; 6 (3; 10)	8; 6 (2; 16)	5; 5 (5; 5)	8; 7 (2; 16)	5; 5 (3; 7)	9; 7 (2; 16)	10; 10 (10; 10)	8; 6 (2; 16)	0.702	0.522	0.431	–

Table 2. Mortality in the group of patients

		Exitus			0–7 days mortality		8–28 days mortality		29–50 days mortality		Statistical analysis			
		Total	Yes	No	Yes	No	Yes	No	Yes	no	Exitus	0–7 days mortality	8–28 days mortality	29–50 days mortality
N		14	7	7	2	12	4	8	1	7	p-value	p-value	p-value	p-value
SCORTEN at admission	2	4 (29%)	1 (14%)	3 (43%)	1 (50%)	3 (25%)	0	3 (38%)	0	3 (43%)	0.464	0.635	0.187	–
	3	3 (21%)	2 (29%)	1 (14%)	0	3 (25%)	1 (25%)	2 (25%)	1 (100%)	1 (14%)				
	4	5 (36%)	3 (43%)	2 (29%)	1 (50%)	4 (33%)	2 (50%)	2 (25%)	0	2 (29%)				
	5	2 (14%)	1 (14%)	1 (14%)	0	2 (17%)	1 (25%)	1 (13%)	0	1 (14%)				

caused by these pathogens was recorded in a total of 9 patients. The maximum dose of methylprednisolone in patients diagnosed with a gram-negative infection within 48 hours of admission to our clinic was 818 mg, whereas the maximum dose of methylprednisolone in patients without this infectious complication was 2,050 mg (p = 0.012); we can, therefore, again see a statistically significantly higher occurrence of infectious complications in patients with lower doses of methylprednisolone. No other statistically significant differences between the groups were detected.

Relationship of the disease severity and other risk factors to the development of infectious complications

SCORTEN was used for evaluating TEN severity. The risk of developing infectious complications increases with the severity of the underlying disease. Nevertheless, none of the parameters studied in our cohort was statistically significant.

Other risk factors for the development of infectious complications in patients with TEN included the length of hospitalization or duration of mechanical ventilation. The average length of hospital stay in patients with multifocal infection was 28 days, and the length of ICU stay was 24 days. In patients without multifocal infection, the average length of hospital as well as ICU stay was 7 days. A statistically significant difference was observed for both parameters in both the total length of hospital stay (p = 0.019) and of ICU stay (p = 0.019). Interestingly, a significant difference was observed also in the length of ICU stay between patients with and without gram-negative bacteria infection within 48 hours of the start of hospitalization in our clinic. Patients with gram-negative bacterial infection spent an average of 27 days in the ICU, patients without these complications had an average ICU stay of only 9 days (p = 0.005).

Another significant difference was detected for the presence of infectious complications caused by both gram-positive and gram-negative bacteria strains between days 2 and 7 of hospitalization. In patients with positivity of this observation, the mean duration of mechanical ventilation was 10 days, while the mean duration of mechanical ventilation in patients with no evidence of infection with gram-positive or gram-negative bacterial strains was only 3 days (p = 0.046). The effect of risk factors such as the total length of hospital stay, time spent in the ICU or MV, and its length on the development of infectious complications during hospitalization is shown in table 3.

The spectrum of potentially pathogenic organisms (PPMs) involved in the development of infectious complications of patients in the cohort

Patients with TEN are confronted with a variety of PPMs on a daily basis. In total, 498 PPMs were isolated in our patient group. Of these, 155 pathogens were gram-positive bacteria (31.1%), 331 gram-negative bacteria (66.5%), and 12 were yeasts (2.4%). The G+/G- ratio was 1:2.14. No filamentous fungi were isolated from any of the patients in the cohort. In the surviving patients, 104 gram-positive bacteria (29.6%) and 240 gram-negative bacteria (68.2%) were cultured, and the G+/G- ratio was 1:2.31. A total of 51 gram-positive bacteria and 91 gram-negative bacteria (62.3%) were cultured from patients who died, the G+/G- ratio was 1:1.78. The dominant PPMs in all studied subgroups were as follows: coagulase-negative *Staphylococci* (121 times), *Klebsiella* sp. (*Klebsiella pneumoniae, Klebsiella oxytoca,* 93 times), *Enterobacter* sp. (*Enterobacter aerogenes, Enterobacter cloacae*, 73 times), and *Pseudomonas aeruginosa* (63x). All cultured PPMs in cohort are shown in Table 4.

The most frequent infectious complication in our patient cohort was infection in the exfoliated wounds, observed in 13 patients. The predominant causative pathogen was coagulase-negative staphylococci (10 patients), followed by *E. coli* (6 patients), *K. pneumoniae* (6 patients), and *A. baumannii* (5 patients). Infections in other anatomical sites were less common. Respiratory tract infections occurred in 6 patients, with *K. pneumoniae*, *P. aeruginosa*, and *Enterobacter* spp. each isolated from 2 patients. Among bloodstream infections (8 patients), coagulase-negative staphylococci were most prevalent (6 patients), while *Enterobacter* spp., *K. pneumoniae*, *S. aureus*, and *Enterococcus faecalis* each accounted for 2 patients. For urinary tract infections, *P. aeruginosa* was the most frequently identified pathogen (6 patients), followed by *K. pneumoniae* (5 patients) and *E. coli* (4 patients). Notably, 4 patients had co-infections involving yeast alongside bacterial pathogens (*P. aeruginosa*, *K. pneumoniae*, or *Enterococcus faecium*).

The level of resistance to antimicrobials in PPMs isolated in patients with TEN

Due to limited numbers, cumulative monitoring was preferred. It was assumed that over the course of the therapy, particularly due to selection pressure elicited by individual antimicrobials, antibiotic resistance would increase. However, we have only observed this in some PPMs; in others, there was no change in the level of resistance.

The sensitivity/resistance of PPMs to key antimicrobials was monitored. Of gram-positive bacteria, the only increase in resistance during hospitalization was observed for coagulase-negative *Staphylococci* whose resistance to oxacillin, clindamycin, and trimethoprim-sulfamethoxazole increased. A total of 58% of all coagulase-negative *Staphylococci* strains isolated within 48 hours of admission were sensitive to oxacillin. However, as early as in week 4, 100 % of coagulase-negative *Staphylococci* strains were resistant to oxacillin. With clindamycin, the situation was similar. In the first 48 hours, 77% of coagulase-negative *Staphylococci* strains were sensitive to this antibiotic.

Table 3. Morbidity and mortality according to the length of ICU stay and mechanical ventilation

			Lenght of stay	Days in ICU	Mechanical ventilation		Days of MV	Statistic evaluation			
		Total	In days	In days	Yes	No	In days	Lenght of stay	Days in ICU	MV	Days of MV
N		14	14	14	11	3	14	p-value	p-value	p p-value	p-value
Infection	yes	14	24; 25 (5; 43)	21; 21 (5; 43)	11 (79%)	3 (21%)	8; 7 (0; 30)	–	–	–	–
	no	0	–	–	0	0	–				
Multifocal infection	yes	11	28; 31 (8; 43)	24; 24 (8; 43)	8 (73%)	3 (27%)	9; 7 (0; 30)	**0,019**	**0,019**	1,000	1,000
	no	3	7; 7 (5; 9)	7; 7 (5; 9)	3 (100%)	0	7; 7 (5; 9)				
< 48 hours infection	yes	12	26; 29 (5; 43)	23; 24 (5; 43)	9 (75%)	3 (25%)	8; 7 (0; 30)	0,170	0,170	1,000	0,645
	no	2	9; 9 (8; 9)	9; 9 (8; 9)	2 (100%)	0	8; 8 (7; 9)				
< 48 hours G+ infection	yes	9	27; 26 (7; 43)	23; 23 (7; 43)	7 (78%)	2 (22%)	10; 7 (0; 30)	0,256	0,316	1,000	0,590
	no	5	17; 9 (5; 34)	16; 9 (5; 31)	4 (80%)	1 (20%)	6; 7 (0; 9)				
< 48 hours G- infection	yes	9	29; 31 (9; 43)	27; 26 (9; 43)	7 (78%)	2 (22%)	10; 8 (0; 30)	0,061	**0,005**	1,000	0,419
	no	5	14; 8 (5; 42)	9; 8 (5; 14)	4 (80%)	1 (20%)	6; 7 (0; 9)				
< 48 hours fungal infection	yes	3	30; 41 (5; 43)	29; 38 (5; 43)	2 (67%)	1 (33%)	3; 4 (0; 5)	0,483	0,391	1,000	0,071
	no	11	22; 24 (7; 42)	18; 19 (7; 31)	9 (82%)	2 (18%)	10; 8 (0; 30)				
Infection 2–7 days	yes	11	23; 26 (7; 43)	22; 23 (7; 43)	9 (82%)	2 (18%)	9; 8 (0; 30)	0,815	0,310	1,000	0,181
	no	3	24; 24 (5; 42)	14; 14 (5; 24)	2 (67%)	1 (33%)	4; 5 (0; 7)				
G+ infection 2–7 days	yes	10	23; 23 (7; 43)	21; 21 (7; 43)	9 (90%)	1 (10%)	10; 9 (0; 30)	0,944	0,723	0,176	**0,046**
	no	4	26; 28 (5; 42)	19; 19 (5; 31)	2 (50%)	2 (50%)	3; 3 (0; 7)				
G- infection 2–7 days	yes	10	23; 23 (7; 43)	21; 21 (7; 43)	9 (90%)	1 (10%)	10; 9 (0; 30)	0,944	0,723	0,176	**0,046**
	no	4	26; 28 (5; 42)	19; 19 (5; 31)	2 (50%)	2 (50%)	3; 3 (0; 7)				
Fungal infection 2–7 days	yes	2	20; 20 (9; 31)	20; 20 (9; 31)	1 (50%)	1 (50%)	5; 5 (0; 9)	0,855	0,855	0,396	0,645
	no	12	24; 25 (5; 43)	21; 21 (5; 43)	10 (83%)	2 (17%)	9; 7 (0; 30)				
Infection 8–14 days	yes	9	32; 31 (19; 43)	28; 26 (14; 43)	6 (67%)	3 (33%)	9; 7 (0; 30)	–	–	–	–
	no	0	–	–	0	0	–				
G+ infection 8–14 days	yes	8	31; 31 (19; 43)	29; 29 (19; 43)	6 (75%)	2 (25%)	10; 8 (0; 30)	–	–	–	–
	no	1	42	14	0	1 (100%)	0				
G- infection 8–14 days	yes	7	31; 31 (19; 43)	29; 26 (19; 43)	6 (86%)	1 (14%)	11; 8 (0; 30)	0,462	0,462	0,083	0,074
	no	2	37; 37 (31; 42)	23; 23 (14; 31)	0	2 (100%)	0; 0 (0; 0)				
Fungal infection 8–14 days	yes	1	42	14	0	1 (100%)	0				
	no	8	31; 31 (19; 43)	29; 29 (19; 43)	6 (75%)	2 (25%)	10; 8 (0; 30)				
Infection 15–21 days	yes	8	34; 33 (24; 43)	29; 29 (14; 43)	5 (63%)	3 (38%)	7; 6 (0; 30)				
	no	0	–	–	0	0	–				
G+ infection 15–21 days	yes	8	34; 33 (24; 43)	29; 29 (14; 43)	5 (63%)	3 (38%)	7; 6 (0; 30)				
	no	0	–	–	0	0	–	–	–	–	–
G- infection 15–21 days	yes	7	33; 31 (24; 43)	31; 31 (23; 43)	5 (71%)	2 (29%)	8; 7 (0; 30)	–	–	–	–
	no	1	42	14	0	1 (100%)	0	–	–	–	–
Fungal infection 15–21 days	yes	1	42	14	0	1 (100 %)	0	–	–	–	–
	no	7	33; 31 (24; 43)	31; 31 (23; 43)	5 (71%)	2 (29%)	8; 7 (0; 30)	–	–	–	–
Infection 22–28 days	yes	6	34; 33 (24; 43)	32; 31 (24; 43)	4 (67%)	2 (33%)	8; 6 (0; 30)	–	–	–	–
	no	0	–	–	0	0	–	–	–	–	–
G+ infection 22–28 days	yes	5	35; 34 (24; 43)	32; 31 (24; 43)	4 (80%)	1 (20%)	10; 7 (0; 30)	–	–	–	–
	no	1	31	31	0	1 (100%)	0				
G- infection 22–28 days	yes	6	34; 33 (24; 43)	32; 31 (24; 43)	4 (67%)	2 (33%)	8; 6 (0; 30)				
	no	0	–	–	0	0	–				
Fungal infection 22–28 days	yes	1	24	24	1 (100%)	0	7				
	no	5	36; 34 (31; 43)	34; 31 (26; 43)	3 (60%)	2 (40%)	8; 4 (0; 30)				

Table 4. All cultured PPMs in the patients in the cohort

Patogen	Survived (n = 7)	Died (n = 7)	Total
Gram-positive bacteria	**104** (67.1%)	**51** (32.9%)	**155**
Coagulase negative *Staphylococci*	**74** (58.2%)	**47** (38.8%)	**121**
Staphylococcus aureus	**4** (100%)	**0** (0%)	**4**
Enterococcus faecalis	**8** (71.4%)	**4** (28.6%)	**14**
Enterococcus faecium	**2** (100%)	**0** (0%)	**1**
Streptococcus sp.	**13** (100%)	**0** (0%)	**13**
Clostridium difficile	**1** (100%)	**0** (0%)	**1**
Gram-negative bacteria	**240** (72.5%)	**91** (27.5%)	**331**
Pseudomonas aeruginosa	**52** (82.5%)	**11** (17.5%)	**63**
Klebsiella sp.	**41** (44.1%)	**52** (55.9%)	**93**
Enterobacter sp.	**73** (100%)	**0** (0%)	**73**
Acinetobacter sp.	**4** (30.8%)	**9** (69.2%)	**13**
Escherichia coli	**20** (80%)	**5** (20.0%)	**25**
Proteus sp.	**29** (78.4%)	**8** (21.6%)	**37**
Citrobacter sp.	**13** (69.2%)	**4** (30.8%)	**13**
Morganela morganii	**0** (0%)	**2** (100%)	**2**
Stenotrophomonas maltophilia	**8** (100%)	**0** (0%)	**8**
Burholderia cepacia	**1** (100%)	**0** (0%)	**1**
Seratia marcescens	**3** (100%)	**0** (0%)	**3**
Yeasts	**8** (66.7%)	**4** (33.3%)	**12**
Candida albicans	**5** (62.5%)	**3** (37.5%)	**8**
Candida parapsilosis	**2** (66.7%)	**1** (33.3%)	**3**
Candida tropicalis	**1** (100%)	**0** (0%)	**1**

By week 4, only 7% of strains were sensitive. Declining effectiveness against coagulase-negative *Staphylococci* was observed for trimethoprim-sulfamethoxazole as well, with 71% sensitivity in the first 48 hours and only 40% by Week 4. All isolated strains retained 100% vancomycin sensitivity. High efficacy against coagulase-negative strains of *Staphylococci* was also observed for tetracyclines (87% in the first 48 hours from the start of hospitalization and 93% at Week 4).

Several interesting findings were observed for gram-negative bacteria as well. An increasing trend in the resistance of *Proteus* sp. strains to aminoglycosides (gentamicin and amikacin) as well as to fluoroquinolones (ciprofloxacin) was observed. A decline in the sensitivity of *Escherichia coli* to aminopenicillins was also detected during hospitalization: in the period of the first 48 hours, a total of 57% of all strains were sensitive, while in Week 2, the level of sensitivity decreased to 25% of isolated strains. A complete overview of antibiotic resistance is shown in table 5.

DISCUSSION

Due to the rarity of this disease, 14 patients with TEN represent the highest number of patients treated in a single center in the Czech Republic and Slovakia in the studied period. Even in the epidemiological studies published so far, the number of patients is quite competitive with already published studies. This study is also the first to systematically address antimicrobial resistance in isolated pathogens in patients with TEN.

The incidence of TEN reported in most epidemiological studies is approx. 0.5–2.0 cases per million population per year [9, 10]. The mortality of patients with TEN is highly variable. Most epidemiological studies report mortalities in the range of 30–50%; however, some suggest even higher mortality [11, 12].

All studies agree that the risk of developing this syndrome increases with age. Older patients have a higher consumption of medications, both chronically and acutely used. The mean age of patients in our cohort was 50.0 ± 24.8 years. This is consistent with multiple epidemiological studies; for example, Haber et al. reported a mean age of 47.7 ± 17.6 years, Brand et al. 50.7 ± 15.7 years, and Struck et al. 56.0 ± 14.0 years [13, 14]. The age distribution of the patients in the cohort is, however, also interesting. Patients included in this cohort were either younger than 33 years or older than 66 years. Similarly, no patient younger than 20 years was hospitalized. The small number of patients makes it impossible to draw firm conclusions, but the same distribution was also observed when analyzing the results of the CELESTE study [15,16]. For reasons that are not yet well defined, most epidemiological studies agree that women are more frequently affected than men (79 % in our cohort, identical to the percentage reported by Struck et al [17].

Table 5. Complete overview of all antibiotic resistance

	Number of patients with positive culture	Number of sp.	Cumulative sum of sp.	Oxacilin			Clindamycin			Tetracyclin			Co-trimoxazole			Aminopenicilin		
				sensitive			sensitive			sensitive			sensitive			sensitive		
		sum	average; median	(cum.)	average; median	medián	(cum.)	average; median	medián	(cum.)	average; median	medián	(cum.)	average; median	medián	(cum.)	average; median	medián
	N	(cum.)	(min; max)	N (%)	(min; max)	of rezist.	N (%)	(min; max)	of rezist.	N (%)	(min; max)	of rezist.	N (%)	(min; max)	of rezist.	N (%)	(min; max)	of rezist.
PATOGENY G+																		
SKN – G+ koagulasa nega. Stafyloccoci				Friedmann's ANOVA: p = **0.008***			Friedmann's ANOVA: p = 0.416			Friedmann's ANOVA: p = 0.145			Friedmann's ANOVA: p = 0.326					
48 h. – 1 week	N = 5	51	10.2; 7.0 (1; 23)	25 (49 %)	0.54; 0.61 (0.0; 1.0)		36 (71 %)	0.66; 0.96 (0.0; 1.0)		42 (82 %)	0.90; 1.00 (0.5; 1.0)		30 (59 %)	0.59; 0.91 (0.0; 1.0)				
1 – 2 week		76	15.2; 10.0 (3; 31)	25 (33 %)	0.31; 0.33 (0.0; 0.6)		50 (66 %)	0.52; 0.42 (0.0; 0.9)		59 (78 %)	0.87; 1.00 (0.5; 1.0)		34 (45 %)	0.40; 0.33 (0.0; 0.9)				
2 – 3 week		88	17.6; 10.0 (4; 37)	27 (31 %)	0.28; 0.25 (0.0; 0.6)		60 (68 %)	0.52; 0.50 (0.0; 0.9)		68 (77 %)	0.87; 1.00 (0.4; 1.0)		36 (41 %)	0.37; 0.25 (0.0; 0.9)				
3 – 4 week		103	20.6; 13.0 (5; 38)	27 (26 %)	0.24; 0.20 (0.0; 0.5)		61 (59 %)	0.45; 0.39 (0.0; 0.9)		82 (80 %)	0.89; 1.00 (0.5; 1.0)		42 (41 %)	0.35; 0.21 (0.0; 0.7)				
ENFA – G+ *Enterococcus feacalis*				* results diffent in 1. and 4. week: p = **0.020**						Friedmann's ANOVA: p = 1.000								
48 h. – 1 week	N = 2	2	1.0; 1.0 (1; 1)							1 (50 %)	0.50; 0.50 (0.0; 1.0)							
1 – 2 week		4	2.0; 2.0 (1; 3)							1 (25 %)	0.50; 0.50 (0.0; 1.0)							
3 – 4 week		5	2.5; 2.5 (1; 4)							1 (20 %)	0.50; 0.50 (0.0; 1.0)							
STR-A,B – G+ *Streptococcus alfa, beta hemolyticus*							Friedmann's ANOVA: p = 1.000			Friedmann's ANOVA: p = 1.000								
48 h. – 1 week	N = 3	5	1.7; 1.0 (1; 3)				4 (80 %)	0.67; 1.00 (0.0; 1.0)		4 (80 %)	0.67; 1.00 (0.0; 1.0)							
1 – 2 week		9	3.0; 1.0 (1; 7)				8 (89 %)	0.67; 1.00 (0.0; 1.0)		8 (89 %)	0.67; 1.00 (0.0; 1.0)							
3 – 4 week		13	4.3; 1.0 (1; 11)				12 (92 %)	0.67; 1.00 (0.0; 1.0)		12 (92 %)	0.67; 1.00 (0.0; 1.0)							
PATOGENY G-																		
PRMI/PRVU – G- *Proteus mirabilis, Proteus vulgaris*													Friedmann's ANOVA: p = 0.392					
48 h. – 1 week	N = 3	22	7.3; 3.0 (1; 18)										18 (82 %)	0.33; 0.00 (0.0; 1.0)				
1 – 2 week		25	8.3; 5.0 (1; 19)										19 (76 %)	0.33; 0.00 (0.0; 1.0)				
2 – 3 week		30	10.0; 6.0 (5; 19)										19 (63 %)	0.33; 0.00 (0.0; 1.0)				
3 – 4 week		33	11.0; 7.0 (7; 19)										20 (61 %)	0.38; 0.14 (0.0; 1.0)				
ESCO – G- *Escherichia coli*																Friedmann's ANOVA: p = 0.317		
48 h. – 1 week	N = 5	18	3.6; 1.0 (1; 11)													14 (78 %)	0.50; 0.50 (0.0; 1.0)	
1 – 2 week		19	3.8; 1.0 (1; 11)													14 (74 %)	0.48; 0.40 (0.0; 1.0)	
PSAE – G- *Pseudomonas aeruginosa*																		
48 h. – 1 week	N = 2	11	5.5; 5.5 (5; 6)															
1 – 2 week		34	17.0; 17.0 (7; 27)															
2 – 3 week		42	21.0; 21.0 (13; 29)															
3 – 4 week		43	21.5; 21.5 (14; 29)															
KLPN/KLOX – G- *Klebsiella pneumoniae, Klebsiella oxytoca*																		
48 h. – 1 week	N = 4	18	4.5; 4.0 (1; 9)															
1 – 2 week		43	10.8; 7.5 (1; 27)															
2 – 3 week		59	14.8; 10.5 (3; 35)															
3 – 4 week		66	16.5; 11.0 (6; 38)															
ENCL/ENAE – G- *Enterobacter cloacae/aerogenes*																		
48 h. – 1 week	N = 2	28	14.0; 14.0 (6; 22)															
1 – 2 week		52	26.0; 26.0 (6; 46)															
2 – 3 week		54	27.0; 27.0 (7; 47)															
3 – 4 week		56	28.0; 28.0 (8; 48)															

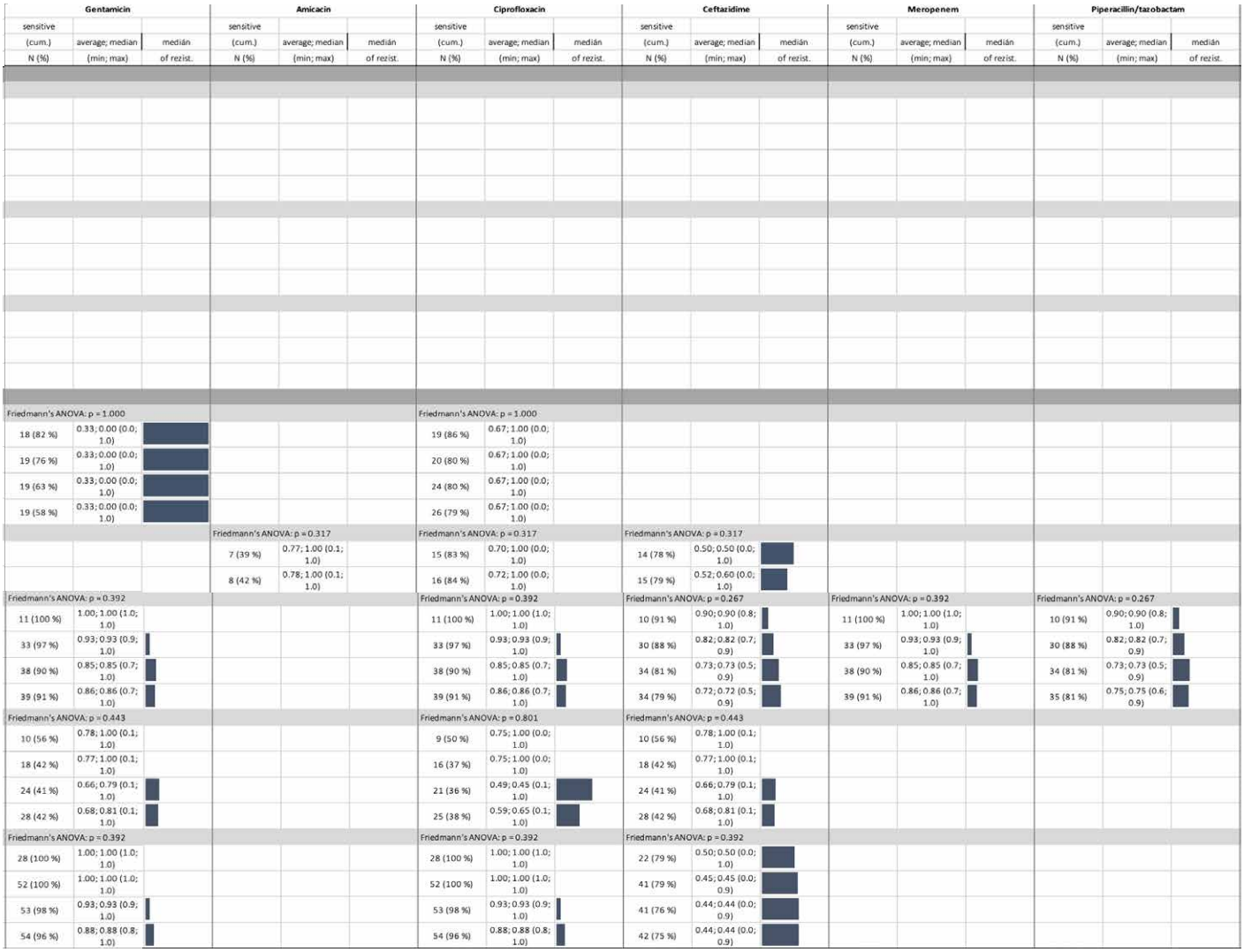
There are several fundamental reasons why they are TEN patients are confronted with a range of pathogens and why they often fail in this confrontation. The basic problem lies in the extensive loss of skin cover, where the local barrier function fails. Mucosal involvement becomes a similar problem, especially when the mucosa of the lower respiratory tract and/or intestinal mucosa are affected. Compromising of the immunological response to PPM invasion due to pharmacologically induced immunosuppression is another reason [16].

The high risk of developing infectious complications in TEN patients has been known for several decades. One of the pioneering papers in this regard was published in 1987 [18]. Revuz et al. followed a very large group of TEN patients (N = 87), of which 20 patients died. Half of them had positive hemoculture (*Staphylococcus aureus*, *Pseudomonas aeruginosa*).

In view of the above, it is not surprising that septic complications are very common in patients with TEN. Khoo et al. reported that in their cohort, up to 61% of patients with TEN met the criteria for sepsis [19].

Gravante et al. investigated the correlation between the positivity of cultures from exfoliated areas and the bloodstream for pathogens. In total, they followed 32 patients with a histologically confirmed diagnosis of TEN. Of this number, 11 patients (34%) died. Positive bacterial isolation from exfoliated areas was observed in 25/32 patients (8/11 deceased, 17/21 survivors) in their study and positive hemoculture in 18/32 patients (7/11 deceased, 11/21 survivors). The study concluded that the presence of more than two different strains of bacteria isolated from hemoculture was significantly associated with death in the cohort ($p < 0.05$) [20].

Prost et al. built on the previous study by monitoring bacteremia in a much larger cohort of adult patients [21]. He followed 179 patients (53 Steavens-Johnson syndom (SJS), 60 overlap TEN, 66 patients with TEN) over eleven years. Interestingly, a very low SCORTEN



was observed in the cohort of surviving patients (median value of 1), while the median value of 3 was observed in deceased patients. This also corresponds to a relatively low mortality rate in their study (13.4%), not to mentinon including SJS a overlap into statistic evaluation. One of the aims of this study was to determine risk factors for the development of bloodstream infection in patients with epidermal necrolysis. These risk factors included the age over 40 years (HR 2.5; 95% IS, 1.35-4.63 p = 0.004) and the extent of exfoliated area exceeding 30% TBSA (HR 2.5; 95% IS, 1.13-5.47 p = 0,023). Interestingly, the positivity of culture from exfoliated areas for methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* strains also led to a statistically significant role of *Enterobacteriales* in the development of bloodstream infection. This confirms the hypothesis that patients with a larger extent of skin exfoliation also suffer more frequently from mucosal involvement, which leads to reduced intestinal barrier competence and, potentially, to a higher likelihood of bacterial translocation from the endoluminal space into the bloodstream.

Probably the most comprehensive discussion of microbiological issues and antimicrobial policy in patients with SJS or TEN was published in 2016 [22]. The study was conducted on 24 patients (only 5 patients had a confirmed diagnosis of histologically) in whom 303 materials were cumulatively collected for culture. Of those, 113 samples (37.3%) were positive. Most frequent positivities were found in the exfoliated area (52 times), hemoculture cultures (25 times), 14 positive of lower respiratory tract material. In contrast to our cohort, a predominance of gram-positive bacterial strains was found in their study.

From the available publications, it can be said that infectious complications develop in 62.9%–91.7% of patients with SJS or TEN, the infections in the exfoliated area occur in from 31.8%–78.0%, and bloodstream

infections in 14.8%–54.2% of patients [23, 24, 25, 26]. Data regarding the incidence of infectious complications in other compartments are not currently available.

CONCLUSION

Toxic epidermal necrolysis remains a rare disease accompanied by high mortality. Unfortunately, the rarity of this disease does not allow verification of any therapeutic concept in a larger cohort of patients in a relatively short period of time. This is the first publication ever to address not only antimicrobial resistance in isolated pathogens in patients with TEN but also the dynamics of changes in antimicrobial resistance of pathogens isolated from TEN patients.

Study limitation

The limitation of our study can certainly be seen as the size of the study population in contrast to the large amount of data collected. It is worth mentioning here that despite the small number of patients, this is still a large and relatively unique set of patients with TEN. Another limitation is undoubtedly the fact that this is a monocentric study. Furthermore, the large dispersion of patients over a long timeline has undoubtedly had an impact on the options and treatment of these patients. However, this is also due to the rarity of the diagnosis.

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Conflict of interest
All authors declare that there are no conflicts of interest with respect to this paper.
All the authors declare that the study presented in the manuscript does not have any potential conflicts of interest, including employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

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