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Toxic epidermal necrolysis and Steven Johnson syndrome: 11-years experience and outcome

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Abstract. – ***Background and Objective:*** **Toxic epidermal necrolysis and Steven Johnson syndrome are rare diseases that usually follow drug-exposures. The authors present one retrospective study with their management and focus their retrospective analysis on finding prognostic factors.**

Materials and Methods: **We reviewed charts of admitted patients from January 1995 to December 2005. Only those with an histologic-proved diagnosis were included in the study. Causative drugs, symptoms, management and outcome were recorded and analysed.**

Results: **We found 32 patients that met inclusion criteria. Mortality rate was 34.4% (11/32). Age, delay of referral, Total Burn Surface Area, white blood cells, creatinine, blood sodium, immunoglobulins therapy and more than two different types of blood bacterial species isolated were significantly correlated with death ($p < 0.05$).**

Conclusions: **These data confirm prognostic factors already present in literature and find that the number of different bacterial species isolated from blood increase mortality. Further prospective studies are necessary to confirm these findings.**

Key Words:

Toxic epidermal necrolysis, Lyell syndrome, Steven Johnson syndrome, Drug reactions.

Introduction

Toxic epidermal necrolysis (TEN), also called Lyell syndrome, is a complex and rare disease (incidence estimated in 0.4-1.2 cases/million of citizens/year) that affects both skin and mucosal surfaces. Although many progresses have been made in the comprehension of cellular and molecular mechanisms underlying pathophysiology, mortality remains severely high involving 30-49% of affected patients[1-3].

The peculiar characteristic of the disease, consisting in a wide detachment of skin and mucosal areas, leads to wide fluid losses and high infection rates. These effects derive from the absence of the barrier function of exposed surfaces and are grossly similar to those present in burn patients. For this reason it's universally accepted that these patients be referred to burn centres for adequate treatment[4-11].

The authors retrospectively reviewed, at the turn of the 11th year, their caseload in the management of this disease. Additionally, they analysed data focusing on factors that could predict the mortality.

Materials and Methods

We retrospectively reviewed the medical charts and the computer database of the admitted patients at the Burn Centre of S. Eugenio Hospital in Rome from January 1995 to December 2005. We included in this study all patients that, after an initial clinical suspicion (wide epidermal and mucosal detached areas following a drug exposure, positive Nikolsky sign), received an histological diagnosis of TEN (full thickness epidermal necrosis with dermo-epidermal detachment). We excluded all burned patients, those with postinfective exfoliative skin conditions, bullous disease of other origins, clinical diagnosis of TEN (not proved with histology) or patients with uncertain histologic results.

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We recorded patients' demographics, delay of referral, comorbid conditions, precipitating event (event that led to drugs being administered), clinical and haematological parameters (fever, Total Body Surface Area of detached skin at first visit – TBSA –, white blood cells, haemoglobin, platelets, blood urea nitrogen, creatinine, sodium, potassium, transaminases), isolation of bacteria during the hospitalization (from wounds, blood and other sites), treatment adopted, length of hospitalization and outcome (death). Hospitilization was defined as the hospital stay only at the authors burn center and not days prior to transfer when the patient was hospitalized elsewhere. Drug/s involved were determined from patient's or parents' history considering all those administered during the previous 8 weeks before symptoms appearance (risk period).

Management Protocol

We developed our protocol over the years. Initial management consisted in the avoidance of all possible drugs and in extreme care in reintroducing only those necessary. A careful history was taken to establish the initiating drug and the precipitating event that rendered drug assumption necessary. Physical examination assessed TBSA. Baseline laboratory tests, chest x-ray films, and skin biopsies were systematically obtained. Sepsis was defined from the presence of clinical (fever) and haematological signs (leukocytosis, positive blood cultures) and wound infections from erythema, pus discharge and positive wound cultures. Samples from wounds and blood were collected for cultures and sent for examination only if clinical and haematological signs of infections (i.e. fever or leucocytosis) were present. Serial pictures were taken in every patient for monitoring and records.

Patient were recovered in intensive care-isolated rooms. Barrier garments and frequent hand washings were used by health care personnel coming in and out of the isolation room. Heparin was routinely introduced for prophylaxis of thromboembolic events. Supportive therapies were adopted according to intensive care protocols as required. When clinical conditions ameliorated and did not require intensive supportive treatments, patients were transferred in normal non-isolated rooms.

A Foley catheter was inserted for urine output monitoring. A femoral catheter for liquids replacement and a nasogastric feeding tube for enteral nutrition were routinely inserted until 1997. In 1997, 2 patients suffered of gastrointestinal hemorrhage during nasogastric tube insertion and one patient died of fatal pulmonary embolism after femoral thrombosis. After these episodes the nourishment was administered by total parenteral nutrition (low osmolarity formulas through a peripheral vein) in the early phase of the disease and by oral supplements later. Basal energy expenditure and metabolic requirements were calculated from the Harris-Benedict's formula. No fluid resuscitation regimens specific of thermal burns were used but fluids were administered according to urine output and estimated insensible loss. Pain control was usually served best with a combination of non steroidal anti-inflammatory drugs (NSAIDs) and/or opioid analgesics. NSAIDs were used only if not suspected of determining TEN and if the patient did not refer any specific allergies. Gastric ulcer prophylaxis was prescribed in the form of proton-pump inhibitors.

Local therapy consisted in a "no touch" approach to avoid any kind of skin damage. Local disinfection was not practised in wounds without clinical signs of infections (erythema, pus discharge) to limit skin detachments. All exposed areas were medicated only with an esterification product of the hyaluronic acid (Jaloskin, Gerke Pharm GmbH, Grevenbroich, Germany) until spontaneous complete coverage was achieved. No other topical treatments were used.

All patients were put in an air-fluidised bed (Clinitron™) until autonomous mobilization was available. An ophthalmologist was usually early consulted for eye care and local lubricants initiated to prevent conjunctival-corneal adhesions (Xanthopterin 2-3 times daily). Chest and legs physical therapy was introduced as soon as possible to prevent pneumonia and deep venous thrombosis.

In 1999 we introduced intravenous immunoglobulins in routine therapy and all patients, starting on February received the same dose and the same duration of treatment (400 mg/kg for 5 days). No patient received steroids.

Statistical Analysis

All data analysis were performed using the Statistical Package for the Social Sciences Windows version 13.0 (SPSS, Chicago, Illinois, USA). Descriptive statistics used for continuous variables, after confirmation of normal distribution (histograms, Q-Q plots, Skewness and Kurtosis, Kolmogorov/Smirnov and

Shapiro Wilk testings), were mean and standard deviation. Descriptive statistics used for discrete variables consisted in frequencies report. Survival analysis was performed with the multivariate model of the Cox regression analysis. All *p* values were considered significant if < 0.05.

Results

We admitted 35 patients with an initial clinical diagnosis of toxic epidermal necrolysis, 32 of them received an histologic confirmation and were analysed in this study (Table I). Year distribution seemed to decrease from 1997 (Figure 1). Initial care was usually administered at peripheral hospitals or from general practitioners and patients were referred to our centre for the progressive worsening of the cutaneous or systemic situation. Mean delay for referral in our institution was 10 days from the symptoms' appearance (standard deviation 10.6, range 0-60).

There were 21 women (65.6% of patients) and 11 men (34.4%). Mean age at diagnosis was 44.8 years (standard deviation 20.23, range 4-94). The most frequent comorbid conditions present were neoplastic diseases (10 patients – 31.3%), followed by infections (5 patients – 15.6%) and recent surgery, within a week to the onset of TEN (4 patients – 12.6%). The most frequent drugs administered at the time of TEN appearance were antibiotics (13 patients – 40.6% – including also antiparasitic and antihelmintic drugs) followed by anticonvulsivants (10 patients – 31.3%) and nonsteroidal antinflammatory drugs (5 patients – 15.6%) (Table II).

A descriptive statistics of patients is summarized in Table III. Steven-Johnson syndrome (SJS – defined as less than 10% of TBSA) was present in one patient and undetermined SJS-TEN overlap form (from 10 to 30% of TBSA) in 7 patients[12]. These forms together accounted for 25% of cases (8 patients). Wound cultures resulted positive for bacterial growth in 25 patients throughout the hospitalization (78.1%) while blood cultures in 19 patients (59.4%). *Staphylococci* accounted for 56% of wound infections and 48% of blood sepsis. Mean length of hospitalization was 17 days (standard deviation 9, range 3-40). There were 11 deaths (34.4% of patients). Two of them occurred in Steven Johnson Syndrome and undetermined SJS-TEN overlap cases (2/8, 25%), 9 of the in TEN patients (9/24, 37.5%).

Survival Analysis

We examined as possible factors influencing death the sex, age, delay for referral to our centre since symptoms appearance, TBSA, white blood cells, creatinine, blood sodium and potassium, immunoglobulins (IgV's) therapy and the number of bacterial species isolated from patients' blood throughout the hospitalization. Both delay of referral and number of bacteria were divided in two groups: for the delay in ≤ 4 days vs. > 4; for isolated bacteria in ≤ 2 vs. > 2. Cox regression analysis demonstrated that age, delay of referral, TBSA, white blood cells, creatinine, blood sodium, IgV's therapy and more than two different types of blood bacteria isolated were significantly correlated with death ($p < 0.05$). In particular, the delay of referral increased mortality probability of 416.5 times, the absence of IgV's therapy of 67.5 times and more than 2 types of bacteria 84 times (Table IV).

Discussion

Toxic epidermal necrolysis (also called Lyell syndrome) is a rare and severe adverse drug-induced skin/mucosal disease. Antibiotics, anticonvulsivants and non-steroidal antiinflammatory are the most commonly involved drugs[12]. Its rarity poses important problems for research, based mainly on retrospective studies, case series or case reports from different burn institutions[13]. Mortality is still high[1-3] and prognostic factors have been summarized in the SCORTEN score[14,15].

We recorded in our centre a high mortality rate (34% of patients) similar to most literature data[1-3,16-19]. The statistical analysis confirmed 3 of the 7 SCORTEN prognostic factors (age, delay of referral and TBSA, creatinine/blood urea nitrogen). Cancer was present in 11 of 32 patients (34.7%). Mortality in these patients was 36.4% (4/11), not significantly different from those not affected (33,3% – 7/21) and overall mortality (34,4% – 11/32). We couldn't specifically investigate the presence of tachycardia at admission as well as blood glucose or bicarbonate because charts of early recovered patients (1995-97) were missing about these data. We included in the

Table I. Demographics and clinical characteristics of recovered patients. Drug 1 is referred to the newly introduced drug, "drug 2" to those already assumed.

Patient no.	*Year*	*Sex*	*Age*	*Burn centre delay of referral (days)*	*Event that led to drug administration*	*Probably involved drug*	*Drugs administered in the 8 weeks preceding TEN*	*TBSA*	*Duration of fever (days)*	*Wound culture*	*Blood culture*	*Other*	*Length of hospitalization (days)*	*Dead (D) or Alive (A)*
1	1995	F	37	10	Hemorrhagic stroke	Deflazacort	–	100	20	*Pseud. Aeruginosa Staph. Aureus*	Negative	*Pseud. Aeruginosa (sputum-lungs)*	10	D
2	1996	F	49	4	Gram- abscess after brain menyngioma surgery	Cefamandole	Carbamazepine Phenobarbital	15	11	–	*Acinetobacter Baumanii Staph. Aureus*	*Acinetobacter Baumanii E. Coli (liquor)*	9	D
3	1997	F	21	12	–	Pyrantel pamoate	Rifaximin	20	30	*Pseud. Aeruginosa Staph. Aureus*	*Enterococcus Faecalis Diphteroids Staph. Aureus Staph. Coag.-*	*Staph. Aureus (oral) Pseud. Aeruginosa (central venous catheter, vagina) Enterococcus Faecalis, E. Coli (vagina)*	*22*	A
4	1997	F	94	8	Flu-like symptoms	Ketoprofen	–	13	2	*Staph. Aureus*	Negative	–	16	A
5	1997	F	19	9	Tension headache	Nimesulide, Paracetamol, Aspirin-	–	70	26	–	*Staph. Aureus Pseud. Aeruginosa*	–	40	A
6	1997	F	4	3	–	Diphtheria-pertussis-tetanus vaccine	Clotrimazole Azythromycin	26	2	*Staph. Coag.-*	Negative	*Staph. Coag-. Acinetobacter Baumanii (urinary catheter)*	12	A
7	1997	M	43	8	Leishmaniasis (HBV,HCV and HIV+)	Amphotericin	Ciprofloxacin, Trimethroprim/ Sulfa-methoxazole, Allopurinol, Itraconazole Paracetamol	90	3	–	*Staph. Coag-*	–	3	D
8	1997	M	31	7	Systemic erythematosus lupus	Ketoprofen	Carbamazepine	35	3	*Staph. Aureus*	*Staph. Coag-*	*Staph. Aureus (conjunctivae)*	15	A
9	1997	M	63	7	Hemorrhagic stroke	Phenobarbital	–	93.5	5	–	*Enterococcus Faecalis Citrobacter Freundii Staph. Coag*	–	11	D
10	1997	F	69	15	Brain astrocytoma	Phenobarbital	–	45	4	–		–	7	A

11	1998	F	66	5	Pleural mesothelioma	Ceftriaxone	Epidoxorubicin Interferon Bromazepam	90	0	*Staph. Aureus Staph. Coag.- Strep. Viridans*	*Staph. Aureus*	–	17	A
12	1998	F	36	10	Sun exposure	Isothipendyl (gel)	–	90	6	*Staph. Coag.-*	Negative	–	12	A
13	1998	F	52	60	Cutaneous mycosis	Terbinafine	–	95	—	*Acinetobacter Baumanii Pseud. Aeruginosa Staph. Aureus*	*Acinetobacter Baumanii Pseud. Aeruginosa Staph. Aureus Proteus Mirabilis Enterococcus Faecalis*	*Pseud. Aeruginosa Staph. Aureus Proteus Mirabilis (central venous catheter)*	5	A
14	1998	F	27	5	Post-transplant chronic renal failure Kaposi's sarcoma	Meropenem	–	21	5	*Staph. Coag.- Enterococcus Faecalis*	*Staph. Coag.-*	–	7	A
15	1998	F	44	5	Glioblastoma	–	–	80	10	*Kl. Pneumoniae*	*Pseud. Aeruginosa Enterobacter Aerogenes Enterococcus Faecalis Staph. Coag.-*	*Pseud. Aeruginosa (mouth)*	30	A
16	1999	M	55	5	Non-Hodgkin lymphoma (HIV+)	Fluconazole, Acyclovir, Trimethroprim/ Sulfa-methoxazole, Allopurinol	–	100	19	*Staph. Aureus, Acinetobacter Baumanii, Staph. Coag-*	*Staph. Aureus, Acinetobacter Baumanii, Staph. Coag-*	*Staph. Aureus, Acinetobacter Baumanii, Pseud. Aeruginosa (central venous catheter)*	19	A
17	1999	F	54	7	Non-Hodgkin lymphoma Cutaneous mycosis	Fluconazole	–	100	2	*Staph.Aureus Pseud. Aeruginosa*	*Staph. Aureus Pseud. Aeruginosa Acinetobacter Baumanii Staph. Coag.- Pseud. Fluorescens*	*Staph. Coag.- (pleural essudate)*	9	D
18	2000	M	62	6	Cirrhosis (HCV+) Chronic Heart Failure	Allopurinol	–	39	0	*Enterococcus Faecalis Staph. Hominis*	–	–	28	D
19	2000	M	58	8	Brain astrocytoma	Phenobarbital	Ciprofloxacin Vancomycin	38	17	*Staph. Aureus*	*Staph. Aureus*	–	32	A
20	2000	F	11	8	Sun exposure	Isothipendyl (gel)	Dimethindene Rokitamycin	83	0	*Staph. Coag.-*	Negative	–	14	A
21	2000	F	30	0	–	–	–	100	0	*Staph. Coag.-*	Negative	–	8	A
22	2001	F	43	8	Flu-like symptoms	Bromhexine	Dextromethorphan	100	0	*Diphteroids Staph. Coag.-*	*Diphteroids Staph. Aureus*	–	14	A

Continued

Table I *(Continued).* Demographics and clinical characteristics of recovered patients. Drug 1 is referred to the newly introduced drug, “drug 2” to those already assumed.

Patient no.	*Year*	*Sex*	*Age*	*Burn centre delay of referral (days)*	*Event that led to drug administration*	*Probably involved drug*	*Drugs administered in the 8 weeks preceding TEN*	*TBSA*	*Duration of fever (days)*	*Wound culture*	*Blood culture*	*Other*	*Length of hospitalization (days)*	*Dead (D) or Alive (A)*
23	2001	F	24	5	Corneal transplant	Deflazacort	Cefazolin	34	4	–	Negative	–	25	A
24	2002	F	74	3	Hemorrhagic stroke	Lansoprazole	Phenytoin Phenobarbital	100	7	*Staph. Aureus*	*Staph. Aureus Enterococcus Faecalis*	–	21	D
25	2002	F	58	6	Prosthesis removal	–	–	22	0	*Providencia Stuartii Enterococcus Faecalis Candida*	*Diphteroids*	–	16	D
26	2002	M	19	30	Systemic erythematosus lupus	Carbamazepine	Azathioprine	100	0	–	–	–	6	D
27	2003	M	44	6	Acute renal failure	Furosemide	Carvedilol	6	0	*Staph. Aureus*	Negative	–	18	A
28	2003	M	62	8	Brain astrocytoma	Sertraline	–	22	8	*Staph. Coag.-*	Negative	–	19	A
29	2004	F	66	19	Abdominal operation	Iron and folate supplements	–	54	15	*Staph. Aureus*	*Staph. Aureus*	–	27	A
30	2004	M	51	9	–	Cefaclor	Rosuvastatin	87	1	*Staph. Coag.-*	–	–	12	D
31	2004	M	26	6	Epilepsy	Carbamazepine	–	35	0	–	Negative	–	34	A
32	2005	F	44	15	Idiopathic myelofibrosis	Metronidazole	Piperacillin	50	7	*Acinetobacter Baumanii, Staph. Aureus*	*Acinetobacter Baumanii*	–	13	D

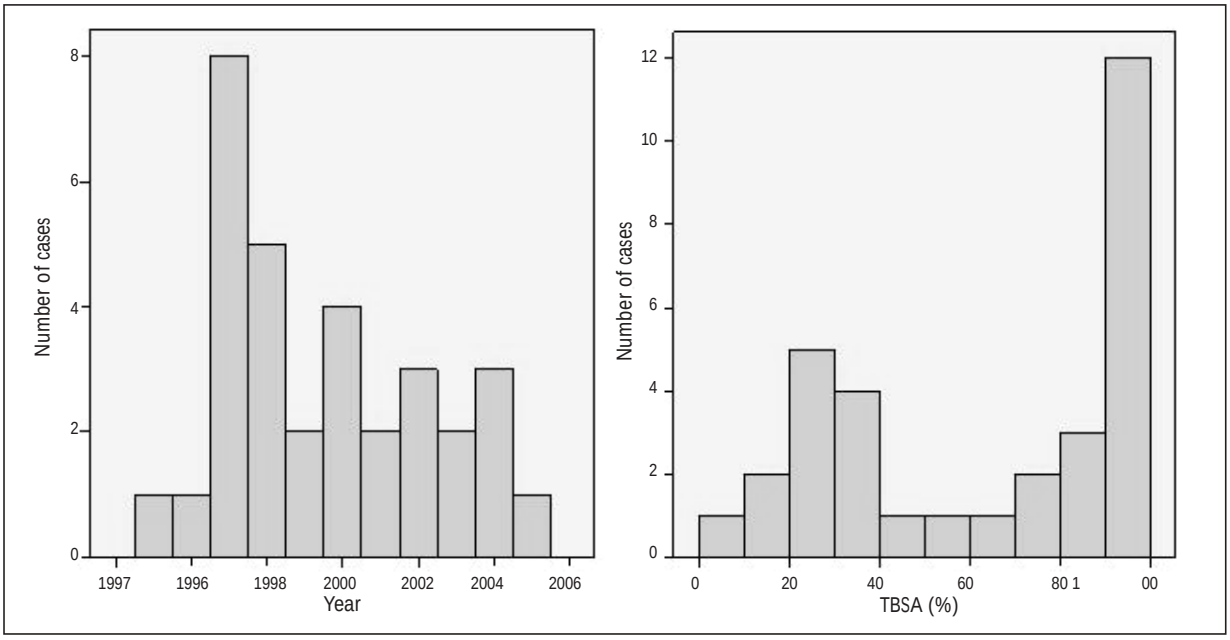

Figure 1. *Left panel*: number of patients from 1995 to 2005. *Right panel*: TBSA distribution of patients.

study both TEN, SJS patients (1 case) and overlapped forms (7 cases) because, at the time of recovery, all of them had wide epidermal and mucosal detached areas following drug exposures, positive Nikolsky signs and same histopathologic appearance of the skin. Specific analysis revealed prognostic differences among TEN (42.1% of mortality) vs. other conditions (25% of mortality). These findings were also confirmed by the Cox regression analysis that found TBSA as a factor influencing death.

A lack of association with mortality was observed for the type of drug theoretically incriminated of TEN's occurrence or with the total number of drugs assumed before hospitalization (data not shown). With particular regard to comorbidities, the statistical analysis did not show a higher mortality if patients were affected by one, two or more comorbidities, neither the analysis by specific diseases (i.e. tumors, strokes, infections) showed a correlation with mortality. We found an interesting prevalence of malignancies in our TEN patients (ten of them – 31.3% – were also affected by tumours). All oncologic patients in general received several drugs possibly involved in TEN pathogenesis (antibiotics, gout-preventing drugs, non steroidal anti-inflammatory drugs). Additionally, brain cancer patients (5 patients) assumed anticonvulsivants to prevent epileptic crisis.

Delay of referral to the burn centre was confirmed as an important prognostic factor at the Cox regression multivariate analysis, contrarily to other authors[15], and had the greatest influ-

Table II. Demographics and clinical characteristics of recovered patients. Drug 1 is referred to the newly introduced drug, "drug 2" to those already assumed.

Comorbidities/ drug	*N. cases*	*Percentage (%)*
Tumor	10	31.3
Infection	5	15.6
Surgery	4	12.5
Stroke	3	9.4
Flu or muscular pain	3	9.4
Renal failure	2	6.3
Sun burn	2	6.3
Viral hepatitis	2	6.3
HIV	2	6.3
SLE	2	6.3
Epilepsy	1	3.1
Antibiotics	13	40.6
Anticonvulsivants	10	31.3
Nonsteroidal antinflammatory drugs	5	15.6
Systemic corticosteroids	2	6.3
Allopurinol	3	9.4
Sunscreen protective creams	2	6.3
Others	7	21.9

Table III. Descriptive statistics of 32 patients.

Variable	Patients (n = 32)
Age	45 ± 20
Sex (male number)	11/32 (34.4%)
Delay of referral	10 ± 11
Number of drugs already on board when TEN started	1.3 ± 0.9
Comorbidities (see Table III)	24/32 (75%)
TBSA (%)	62 ± 34
Presence of fever at hospitalization	22/32 (68.8%)
Duration of fever	7 ± 8
White blood cells (/mL)	8131 ± 6200
Hemoglobin (g/dL)	11.2 ± 2.6
Platelets (/mL × 1000)	225 ± 137
Blood Urea Nitrogen (mg/dL)	63 ± 56
Creatinine (mg/dL)	1.6 ± 2.2
Sodium (mmol/L)	136 ± 8
Potassium (mmol/L)	4.2 ± 1.0
GOT (U/L)	54 ± 63
GPT (U/L)	56 ± 73
IgV's therapy	17/32 (53.1%)
Wound culture positive	25/32 (78.1%)
Different bacteria isolated from wound cultures throughout hospitalization	1.3 ± 1.0
Sepsis	18/32 (56,2%)
Different bacteria isolated from blood cultures throughout hospitalization	1.2 ± 1.5
Length of hospitalization	17 ± 9
Duration of disease	27 ± 12

ence on mortality. If greater than 4 days it increased the risk of death of 416 times. This could be derived from the delay in introducing specific immunoglobulin-blocking therapy and specific support therapy. Furthermore, patients referred late were probably more ill than those referred early. In other words, the late referral delayed introduction of immunoglobulin therapy and represented a failure in management at the preliminary hospital with worse patients outcomes in our center.

Immunoglobulins (IgV's), administered since 1999, seemed to have a positive effect on mortality even in patients with high delays of referral. Although the effect of IgV's therapy on Steven Johnson Syndrome and TEN is not well established and our study was retrospective and not prospective, the absence of IgV's therapy increased the risk of death of 67.5 times. A theoretic interpretation of this can derive from the persistence and activation of CD95 system (the main system inhibited by IgV's)[20-21] even days later from the initial stimulus. However, since IgV's was given to patients after 1999, and not to patients before, differences could be attributable to better care, more experience in TEN management and refinements in TEN protocol that occurred over time rather than a specific effect of immunoglobulins. For this reason, we confirm that the debate about the efficacy of IgV's in TEN patients is still not over and further studies are required to address this question.

Our data confirmed that septicaemia is an important mortality factor. Furthermore, we found that different bacterial species were present and isolated from patients blood, simultaneously or metachronously throughout the hospitalization. The correlation analysis of these data showed a great increase in mortality after 3 or more different bacterial species were isolated during hospitalization. When isolated bacterial species were 3 or more, mortality increased of 84 times. Al-

Table IV. Cox regression analysis of survival. Exp (B): hazard risk.

			95.0% CI for Exp (B)	
	Hazard ratio	Sig. (p)	Lower	Upper
Sex	0.788	0.888	0.028	21.831
Age	1.118	0.042	1.004	1.244
Delay of referral	416.513	0.010	4.325	40109.530
Comorbidities (see Table III)	18.293	0.205	0.204	1640.991
TBSA	1.069	0.021	1.010	1.131
White blood cells	0.999	0.029	0.998	1.000
Creatinine	2.205	0.047	1.012	4.808
Blood sodium	0.714	0.020	0.538	0.949
Blood potassium	0.164	0.085	0.021	1.283
IgV's therapy	–67.491	0.007	3.128	1456.278
> 2 blood bacteria isolated	83.994	0.044	1.121	6295.833

though the design of our study (retrospective analysis, a small population size hospitalized in one burn center, a long delay of referral from other institutions) does not allow drawing any firm conclusion, this data, if confirmed by further studies, could be used as prognostic markers during patient's hospitalization.

In conclusion, although much has been discovered about the etiology and pathogenesis of toxic epidermal necrolysis and new treatments have become available in the last years, mortality is still high. The analysis of our data shows that age, TBSA, white blood cells, creatinine, IgV's therapy and more than two different types of blood bacteria isolated during hospitalization were significantly correlated with death ($p < 0.05$). Further larger studies are necessary to confirm these findings.

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