November 1986
Volume 204, Number 5

Annals of Surgery

Improved Burn Center Survival of Patients with Toxic Epidermal Necrolysis Managed without Corticosteroids

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Fifteen consecutive patients with toxic epidermal necrolysis or the Stevens–Johnson syndrome managed without corticosteroids after transfer to the burn center (group 2) are compared to a previous consecutive group of 15 who received high doses of these drugs (group 1). Group 2 had a 66% survival, which was a significant improvement compared to the 33% survival in group 1 ($p = 0.057$). In group 1, mortality was associated with loss of more than 50% of the body surface area skin. In group 2, mortality was related to advanced age and associated diseases. Age, extent of skin loss, progression of skin loss after burn center admission, incidence of abnormal liver function tests, and the incidence of septic complications were not significantly different in the two groups ($p > 0.10$). The incidence of detected esophageal slough was similar in both groups. Nonsteroid (group 2) management was associated with a decreased incidence of ulceration of gastrointestinal columnar epithelium, Candida sepsis, and an increased survival after septic complications. The combined experience of these 30 patients suggests that corticosteroids are contraindicated in the burn center management of toxic epidermal necrolysis and the Stevens–Johnson syndrome.

Presented at the 16th Annual Meeting of the American Burn Association, April 11, 1984, San Francisco, California.

Supported by the Schatzberg Fund.

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Submitted for publication: April 4, 1986.

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TOXIC EPIDERMAL NECROLYSIS (TEN) is a severe exfoliative dermatologic disorder of unknown etiology that has entered the realm of general surgical practice with the advent of specialized burn centers.[1,2–6] TEN, also known as Lyell's disease,[7] is considered by many to be a severe variant of the Stevens–Johnson syndrome (SJS),[8–10] which may or may not involve preceding erythema multiforme (Fig. 1). Clinically, these patients suffer extensive, painful loss of the epidermis, mucosal ulceration (Fig. 2), and fever. There may be significant morbidity and mortality. High-dose corticosteroid therapy is the most consistently advocated therapeutic intervention. Dosages of 240–1000 mg hydrocortisone equivalents daily are recommended, with the goals of preventing further epidermal involvement and controlling such clinical manifestations as fever and discomfort.[1,2,4,12,13,15]

The first 15 of these patients treated at our burn center received high-dose corticosteroids based on such recommendations (group 1). A previous report documented an unacceptably high mortality from sepsis in these pa-

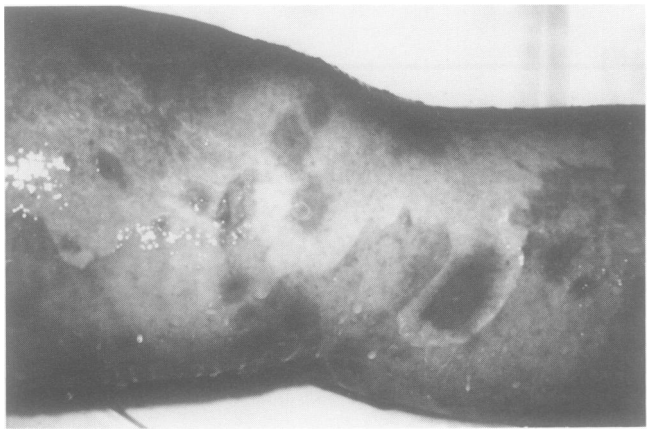

FIG. 1. Admission photograph of the leg of a group 2 survivor who suffered 95% TBSA skin loss. There is the simultaneous appearance of classic targets lesions of erythema multiforme with ulcerations diagnostic of the Stevens–Johnson syndrome and diffuse loss of the epidermis in sheets with a positive Nikolsky sign (displacement of seemingly uninvolved skin with lateral pressure), which is characteristic of toxic epidermal necrolysis.

tients.[16] In many cases, the septic event seemed more virulent than that encountered in similarly injured burn patients. This experience led to a reappraisal of the use of corticosteroids. Since techniques of basic burn care should adequately support patients with extensive cutaneous wounds, all attempts to alter the course of the disease with immunosuppressive therapy were abandoned. Corticosteroids were not instituted, and, if already started at referring institutions, they were discontinued. The initial experience with this protocol was encouraging.[16]

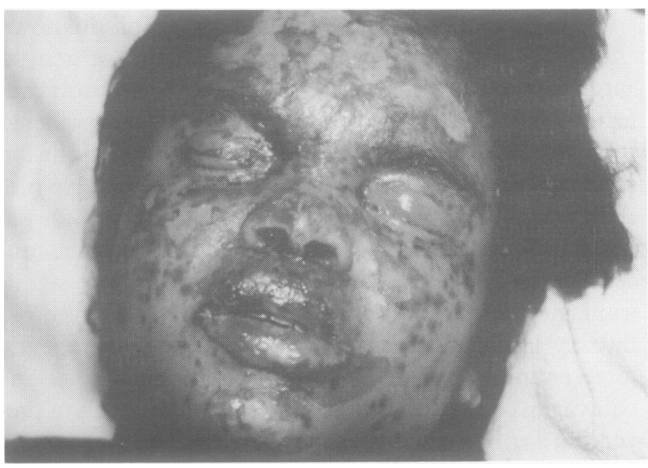

FIG. 2. Typical facial presentation of TEN/SJS. There is extensive ulceration of the oral mucosa causing crusting around the mouth. Corneal slough produces photophobia, causing the patient to keep her eyes closed tightly. Dried serum can act like a tissue glue and should be gently cleared from the lid margins. The conjunctival spaces should be irrigated frequently with ophthalmic solutions and antibiotics to prevent adhesions between the lid and the globe (symblepharons) and secondary infections.

Since that report, 13 additional patients with toxic epidermal necrolysis or Stevens–Johnson syndrome (TEN/SJS) have been admitted, making a total of 15 consecutive patients who have undergone the nonsteroid protocol (group 2). The following report describes the current protocol, presents the clinical characteristics of the recent nonsteroid (group 2) patients, compares these characteristics with those of the earlier steroid-treated (group 1) patients, and finally condemns the continued use of corticosteroids in the management of patients with TEN/SJS severe enough to require care in a burn center.

Methods

The criteria for inclusion were the clinical characteristics of TEN or SJS, a dermal–epidermal cleavage plane on frozen section, and an absence of acantholysis on permanent section of skin obtained by punch biopsy at the time of admission. Biopsies were evaluated by an independent dermatopathologist.

A history of recent new drug intake or symptoms occurring before or at the time of skin or mucosal involvement were sought from all patients, with special reference to upper respiratory infections.

On admission, ruptured bullae and areas of necrotic epidermis that came off easily were debrided. The total extent of skin slough was calculated using a Lund and Browder chart. Mucosal ulcerations were noted as well. Extension of progression of the skin slough was evaluated by comparison with this admission record during subsequent daily dressing changes.

If started at referring institutions, corticosteroids were stopped in the first days after admission. The timing of discontinuance was based on the clinical presentation, the duration and dosage of steroid therapy, and the patient's response to the drastically decreased doses. Concern about adrenal insufficiency (either absolute or relative) was the only factor determining the rate of taper. Specifically, the loss of skin or other manifestations of TEN/SJS had no effect on the timing of steroid discontinuance.

Ringer's lactate was begun on admission in all patients, mainly *via* a peripheral vein. The rate was determined by the patient's condition and urine output. Patients were given a trial of spontaneous voiding, but most required a Foley catheter. In the absence of active sepsis, colloid was administered if serum albumin was less than 2.0 g/dL. Since ileus was uncommon in the absence of sepsis, clinically stable patients were encouraged to begin oral intake from the time of admission.

The preferred primary topical therapy was 0.5% $AgNO_3$ by an occlusive technique. Gauze dressings were changed on a daily basis when the body was gently washed with a dilute (10%) chlorhexidine gluconate (Hibiclens®) in saline solution. Coverage with skin substitutes was indicated for pain relief in patients without complications.

The patients were evaluated prospectively for leukopenia (WBC: 3.4 × 1000), electrolyte abnormalities, and abnormal liver function tests (alkaline phosphatase > 110 U/L, total bilirubin > 1.0 mg/dl, SGOT > 45 U/L, SGPT > 45 U/L) by at least daily laboratory tests during the acute phase of the disease. They were monitored for septic complications by daily cultures of blood, urine, and sputum. Vaginal pharyngeal, conjunctival, and cutaneous wound swab cultures were sent on admission and later as needed.

Autopsies were aggressively sought for all patients who died. Particular attention was directed to the incidence and site of gastrointestinal involvement, occult septic foci, and the integrity of the tracheobronchial mucosa during the postmortem examination. Esophagograms and upper gastrointestinal roentgenograms were performed on survivors with poor oral intake or dysphagia. Early panendoscopy was recommended to all survivors with appropriate symptoms.

Antacids and nystatin were administered enterally every 4–6 hours orally or by feeding tube. Nutritional support was administered enterally to achieve caloric levels calculated by a modified Harris Benedict formula[37] and to prevent weight loss. Parenteral nutrition was reserved for those periods when enteral nutrition was not possible.

Using isolation technique, the patients were cared for in single rooms in the burn unit. They did not share any facilities with burn patients during the acute phase, particularly while still receiving corticosteroids. Care of ocular, oral, and perineal ulcerations was provided four to six times a day with gentle irrigation, using appropriate sterile solutions. Nurses working one on one with the patient were guided by a care plan designed specifically for TEN/SJS.

Invasive monitoring was reversed for specific indications in the critically ill. Intravascular catheters were managed according to recommendations for burn patients.[17] Catheter tips were routinely cultured by quantitative techniques, unless they were obviously contaminated on removal.

The effects of steroid (group 1) *versus* nonsteroid (group 2) therapy on mortality, progression of skin slough after burn unit admission, and incidence of septic complications were assessed by chi square analysis and Fisher's exact test. These two groups were further compared by Student's t-test for age, extent of skin loss, and the length of time from onset of skin lesions until burn unit admission.

Results

All of the patients in group 2, like those in the early group, had extensive areas of confluent epidermal loss, leaving exposed dermis that was extremely tender and erythematous. Mucosal ulceration was present in all patients. The oral and conjunctival surfaces were most frequently involved (Fig. 2), but ulcerations of anal, vaginal, corneal, nasal, and pharyngeal mucosae were often observed as well. Routine histologic evaluation confirmed the diagnosis in every case, with a nonspecific pattern on immunofluorescence staining. Pathologic findings were all consistent with descriptions in the literature.[1,7,18–20]

Autopsies were performed on three of the five patients from group 2 who died. This compares favorably with the rate in group 1, where five of the ten nonsurvivors were autopsied.

Ten patients from group 2 survived, compared to only five from group 1 (Tables 1 and 2) (p = 0.057). Progression of skin slough, a marker of active disease, occurred after admission in nine patients from group 1 and seven patients from group 2. This was not significantly different. Comparison of age (46 ± 6 *vs.* 37 ± 7 years), morbid days before burn center admission, and the amount of skin sloughed (69 ± 6 *vs.* 73 ± 6% total body surface area, TBSA) showed no significant differences between groups 1 and 2, respectively (Table 3).

Four patients from group 2 never received corticosteroids. One of these patients died. In the remaining 11 patients, these drugs were tapered over a mean of 3.4 days. Four of these patients died. Those patients who had a history of chronic steroid use required more time for safe discontinuation. For example, a patient previously treated

TABLE 1. *Survivors*

	Group 1	Group 2	p
N (% total)	5 (33)	10 (66)	0.057
% TBSA skin loss	41 ± 9 (None > 50% loss)	73 ± 8 (7 > 60% loss)	<0.05
Age	45 ± 9	32 ± 9	>0.10
Patients with septic complications	1	4	

TBSA = total body surface area.

TABLE 2. *Mortality*

	Group 1	Group 2	p
Nonsurvivors (%)	10 (66)	5 (33)	0.057
% TBSA slough	84 ± 3	81 ± 9	>0.10
Age	47 ± 8	54 ± 12	>0.10
Cause of death	Sepsis	Sepsis*	
Organism	gram (−) 7 gram (+) 1 (pneumococcal) Candida 2	gram (−) 3 gram (+) 2 (*Staphylococcus aureus*)	

TBSA = total body surface area (epidermal loss).

* Sepsis preceded by acute myocardial infarction and pulmonary embolus in one patient and severe hyperglycemic hypernatremic hyperosmolar coma in one.

TABLE 3. *Clinical Characteristics of All Patients*

	Group 1 (N = 15)	Group 2 (N = 15)	p
Age (years)	46 ± 6	37 ± 7	>0.10
% TBSA slough	69 ± 6	73 ± 6	>0.10
Morbid days prior to BU admission	7.3 ± 0.7	8.3 ± 1.1	>0.10
Progression of slough after admission	9	7	>0.10
Patients with infections	11	9	>0.10
Corticosteroid therapy in BU	High dose	11 patients Taper, d/c 3.5 ± 0.7 days	
		4 patients No steroids	

Results expressed as mean ± SEM.
TBSA = total body surface area (epidermal loss); BU = burn unit.

with steroids who had the onset of skin slough while receiving daily pulse therapy with 1 g of methylprednisolone had steroids discontinued over 7 days, the longest taper in group 2. In contrast, another patient treated with steroids for only 3 days was noted to have a pneumonia on admission and had steroids stopped from the time of admission. This was the most rapid taper in group 2. Only one survivor from group 2 showed symptoms consistent with adrenal insufficiency. This patient received a brief period of stress-dose steroids until Staphylococcus sepsis was documented as the cause of hypotension. Free serum cortisol was 54 μg/dl by radioimmunoassay, a level consistent with the normal adrenal response to sepsis. Four of the five patients who died in group 2 received stress doses of corticosteroids at the time of clinical deterioration because of previous steroid therapy and concern about adrenal insufficiency.

No patient from group 1 who lost more than 50% of TBSA skin survived the injury (Table 1). In marked contrast, seven of the ten survivors from group 2 lost more than 60% TBSA skin (four of these lost 90% TBSA or more). This difference is reflected by the larger mean surface wound in group 2 survivors (73 ± 8% TBSA) compared to group 1 (41 ± 9% TBSA). Group 2 survivors tended to be younger than those from group 1. However, two of them were over 65 years old, with greater than 75% TBSA skin loss.

Nonsurvivors in both groups tended to be older than survivors (Table 2). Both groups of nonsurvivors included a single patient, received in a moribund state of septic shock, who died within 6 hours of admission. Sepsis continued to be the final cause of death in all those who died. In contrast to group 1, two group 2 patients suffered severe nonseptic complications before the onset of sepsis. One patient with severe coronary artery disease suffered a large anteroseptal myocardial infarction. Another patient was transferred in a hyperosmolar coma (glucose: 870 mg/dl, sodium: 176 mg/dl, chloride: 138 mg/dl, admission values) and became septic during the period of fluid and electrolyte correction.

Esophageal slough was detected with equal frequency in both groups (Table 4). Esophageal involvement was documented in one survivor from group 2 by panendoscopy. All of the other findings were made during autopsy. Abnormal liver function tests were also detected with equal frequency. Only one patient from each group demonstrated clinical jaundice; the remainder had mild abnormalities of hepatocellular enzymes or bilirubin. In contrast, gastrointestinal ulcerations distal to the gastroesophageal junction in columnar epithelium were found in five of the 15 patients from group 1 and in only one patient from group 2 (this patient, described earlier suffered from hyperosmolar coma and subsequent sepsis).

Examination of the tracheobronchial mucosa in the three autopsied patients revealed only a localized area of necrosis in the trachea produced by the cuff of the endotracheal tube. No gross or microscopic defects in mucosal integrity were observed distal to this point. Fiberoptic bronchoscopy was performed for pulmonary toilet and placement of nasotracheal tubes during the acute phase in three additional patients. Normal pink tracheobronchial mucosa was observed. This mucosa was not friable and did not bleed, despite aggressive pulmonary toilet.

Small pulmonary emboli were found in two of the three postmortem examinations from group 2 and in one of the five autopsied patients from the early series.

Infectious complications were documented and treated with appropriate intravenous antibiotics in nine of the patients from group 2; five of these were fatal septic processes (Table 5). Gram-negative sepsis caused three of these deaths, one of which was polymicrobial in nature (in the patient mentioned above with hyperosmolar coma and intestinal ulcerations). The other two patients who died suffered from *Staphyloccus aureus* sepsis. One, with methicillin-sensitive Staphylococcus septicemia, arrived in a moribund condition and died within hours of arrival. The other had a methicillin-resistant organism. Two of the survivors were resuscitated from septic shock, which was due in both cases to methicillin-resistant *S. aureus*.

TABLE 4. *Gastrointestinal Involvement*

	Group 1	Group 2
Esophageal slough	2 (Both died)	3 (1 survivor)
GI ulcerations	5	1
Elevated LFT	9	10
Bilirubin > 5	1	1

LFT = liver function tests—bilirubin, SGOT, SGPT, alkaline phosphatase.

The other two had a symptomatic gram-negative lower urinary tract infection. Of the seven patients who had positive blood cultures, five had positive venous catheter tip cultures 24–48 hours before the diagnosis of sepsis was apparent (three with *S. aureus*). Only one of these was a peripheral line. Exploration revealed suppurative thrombophlebitis due to methicillin-resistant *S. aureus,* which required saphenous vein excision. This patient, a survivor, simultaneously developed hematogenous pneumonia and bilateral tension pneumothoraces, which required tube thoracostomies. One patient grew methicillin-resistant *S. aureus* from a central vein catheter tip and subsequently developed Staphylococcus septicemia but survived. Two patients with positive central vein catheter tips and subsequent sepsis who died underwent autopsy. No pus was found in the central veins, but microabscesses were found in the lungs. Blood cultures were positive on admission in five patients from group 2, two of whom died.

Infection occurred with similar frequency in 11 patients from group 1; ten of these were fatal processes. The only survivor from group 1 with documented sepsis suffered from methicillin-resistant *S. aureus* endocarditis. Of the ten who died, two suffered from disseminated Candida sepsis (one of these had an invasive intestinal Candida overgrowth), and one succumbed to pneumococcal sepsis. The other seven patients who died suffered from gram-negative sepsis, which was polymicrobial in three (two of these were autopsied and found to have GI ulcerations). No patient from this group survived septic shock. Four patients from this group had positive blood cultures on admission; all of them died.

Leukopenia was observed in one patient from group 2 in the absence of systemic sepsis and in six patients with sepsis. Two of these had *S. aureus* sepsis and four had gram-negative organisms. In group 1, leukopenia occurred in six patients and was always accompanied by gram-negative sepsis.

Two group 2 patients suffered symptomatic hypernatremia. One, mentioned previously, was in a hyperosmolar coma on admission. The other developed a free-water deficit, which was easily corrected. Hyponatremia, detected frequently in group 2 patients, was corrected in all cases before it became symptomatic. These and other metabolic complications were similar to those in group 1 patients.

There was a history of recent new drug exposures for every patient in both groups. These drugs were usually considered causative for the development of skin slough by referring institutions, although in several cases the exposure was minor or preceded by symptoms that may have been part of the prodrome of TEN/SJS. Drug exposure was similar in the two groups, although Dilantin® and phenobarbital were implicated five times in group 2 and only three times in group 1. This reflects the more frequent history of seizure disorder observed in group 2 (Table 6). The groups were similar in the incidence of chronic autoimmune diseases. Adult onset diabetes mellitus was present in approximately one third of the patients from each group. Symptoms of an upper respiratory infection preceded skin involvement and drug exposure in five of the patients from group 2, compared to three from group 1.

TABLE 5. *Microbiology of Patients with Septic Complications*

Group 1 (N = 11)	Group 2 (N = 9)
Gm (−) sepsis 8	Gm (−) sepsis 5
Polymicrobial 3	Polymicrobial 1
Gm (+) sepsis 2	Gm (+) sepsis 4
(1 *Staphylococcus aureus,* 1 *Streptococcus pneumoniae*)	(All *S. aureus,* 3 MRSA)
Candida sepsis 2	

In group 2, there were 5 IV catheter tip cultures positive for organisms subsequently recovered from blood (4 central lines, 1 peripheral-suppurative thromophlebitis).
MRSA = methicillin-resistant *S. aureus.*

Discussion

A decrease in mortality was achieved in a group of patients managed in the burn center with a protocol that excludes corticosteroids, compared to an earlier group treated with large doses of these drugs. Both groups were similar in terms of age, severity of disease reflected by extent of epidermal loss, and the time between onset and burn center admission. Management without corticosteroids was associated with the survival of more severely injured patients. Infections were documented in approximately two thirds of the patients from both groups, causing a 91% mortality in steroid-treated patients compared to 56% mortality in those not given these drugs. It seems that this improvement in survival resulted from the elimination of an iatrogenic source of mortality rather than an effect on the primary process in TEN/SJS. This con-

TABLE 6. *Associated Diseases*

Group 1 (No. of Patients)	Group 2 (No. of Patients)
AODM (4)	AODM (5)
Seizure disorder (2)	Seizure disorder (5)
Rheumatoid arthritis (1)	Rheumatoid arthritis (1)
SLE (1)	SLE (1)
Goodpasture's syndrome (1)	AIDS + pneumocystis (1)
Granulomatous colitis (1)	Granulomatous colitis (1)
Thoracotomy for trauma (1)	Craniotomy for cerebral aneurysm (1)
Prodromal URI symptoms (3)	Prodromal URI symptoms (5)

AODM = adult onset diabetes mellitus; SLE = systemic lupus erythematosis; AIDS = acquired immunodeficiency syndrome; URI = upper respiratory infection (cough, sore throat).

demnation of corticosteroid use is in agreement with similar reports from other burn centers[5,6] and echoes misgivings occasionally voiced in the dermatologic literature regarding such therapy.[9,17,21,22]

The use of corticosteroids is based on the concept that these disorders are delayed-type hypersensitivity reactions[15,23] and is supported by anecdotal reports, usually of a single patient.[1,2,4,11] In a series of 15 patients described by Bjornberg, hydrocortisone, in doses from 200 to 800 mg, reportedly controlled the epidermal loss and allowed 12 to survive. Two of the in-hospital deaths were due to sepsis.[12] An additional patient rendered cushingoid by months of chronic steroid therapy died suddenly after discharge and was found to have an occult septic focus.[11] While the reported survival is impressive, there was no attempt to compare these patients to control patients managed without steroids. It is difficult to tell the severity of the primary disease, since there was no quantification of skin loss or mucosal involvement. Our own experience would suggest that patients with less than 50% TBSA skin loss are more able to survive high-dose steroid therapy. Rasmussen's review of erythema multiforme in children suggests that, even with minor disorders, increased morbidity is associated with steroid therapy,[22] which may explain why five of Bjornberg's 12 survivors required hospitalization beyond 3 months.[12] All ten survivors from group 2 healed most of their wounds within 14 days of admission. Only one of these patients required hospitalization for more than 3 months (for complications of a suppurative thrombophlebitis). All the rest were ready for discharge less than a month after admission.

Since infections complicated the hospital course of patients from both groups with equal frequency, it appears that improvements in survival in the nonsteroid patients resulted from differences in the type and severity of septic complications and an increased salvage of infected patients, reflecting improved host resistance. Candida sepsis, observed twice in group 1 and noted frequently by others,[5] was notably absent in the nonsteroid group, although oral Candida was found frequently on admission. The liberal use of enteral nystatin may have played a role. Bacterial infections in group 2 were more likely due to *S. aureus* in contrast to the overwhelming incidence of gram-negative sepsis in those receiving steroids. Positive cultures of central venous lines preceded the onset of sepsis in several cases, although suppurative peripheral thrombophlebitis was documented in only one patient. These complications developed despite replacement of the catheter every 72 hours, as recommended by Pruitt.[24]

High-dose corticosteroids markedly suppress the clinical signs of sepsis. It is possible that the improvements in survival noted in group 2 resulted from the earlier detection of septic complications, leading to earlier therapy.

The observation of leukopenia in the absence of sepsis in one patient in group 2 suggests that this is an effect of the primary disease, as suggested by Marvin[6] and Kim.[5] In group 1, leukopenia was always associated with gram-negative sepsis. It is possible that leukopenia associated with TEN/SJS may lead to sepsis. Corticosteroid therapy may alter the leukocyte count. While the etiology of leukopenia is not clear, such a finding demands a thorough evaluation for septic complications.

Ulcerations of the GI tract were detected in one third of the patients in group 1 (Table 4). While the disorder has a predilection for stratified squamous epithelium, which explains esophageal slough, these ulcers were discovered in columnar epithelium. In one patient, such ulcers were the site of invasive candidiasis and may have contributed to polymicrobial sepsis in two others. In the absence of thorough pathologic studies, involvement of cell types other than squamous epithelium has not been ruled out. This raised some concern in implementing the nonsteroid protocol. While cutaneous wounds could be routinely managed, intestinal slough is more difficult. If steroids were mitigating the disease process, cessation might increase the incidence of GI mucosal defects. A recent report confirmed the long-held impression that GI ulcerations are increased during corticosteroid therapy.[25] The lower incidence of such ulcers in group 2 patients supports the hypothesis that they are a consequence of steroid therapy and not the result of the primary disease process, although the lower incidence of septic shock and multisystem failure in group 2 may have contributed to the lower incidence of ulceration.

Mild elevations of liver enzymes were noted with equal frequency in both groups. Jaundice was clinically apparent in only one patient from each group. The mechanism of such dysfunction is not clear, but it may result from the primary disorder rather than from a second process, as suggested by Shaw.[26]

Esophageal slough was found with equal frequency in both groups, further supporting the hypothesis that TEN/SJS may cause slough of any area of stratified squamous epithelium. The specificity of the lesion for squamous epithelium is illustrated in the photomicrograph in Figure 3. This shows a biopsy of the upper esophagus of a group 2 nonsurvivor who had islands of ectopic gastric mucosa present in this area since birth. The mucosal slough has entirely denuded the surrounding esophageal squamous epithelium, while the ectopic columnar epithelium is intact and unaffected despite its location.

The incidence of GI involvement may be underestimated in both groups, since patients do not undergo endoscopic examination on a routine basis. While such examinations are feasible and could probably be performed safely, the presence of oral and pharyngeal ulcerations

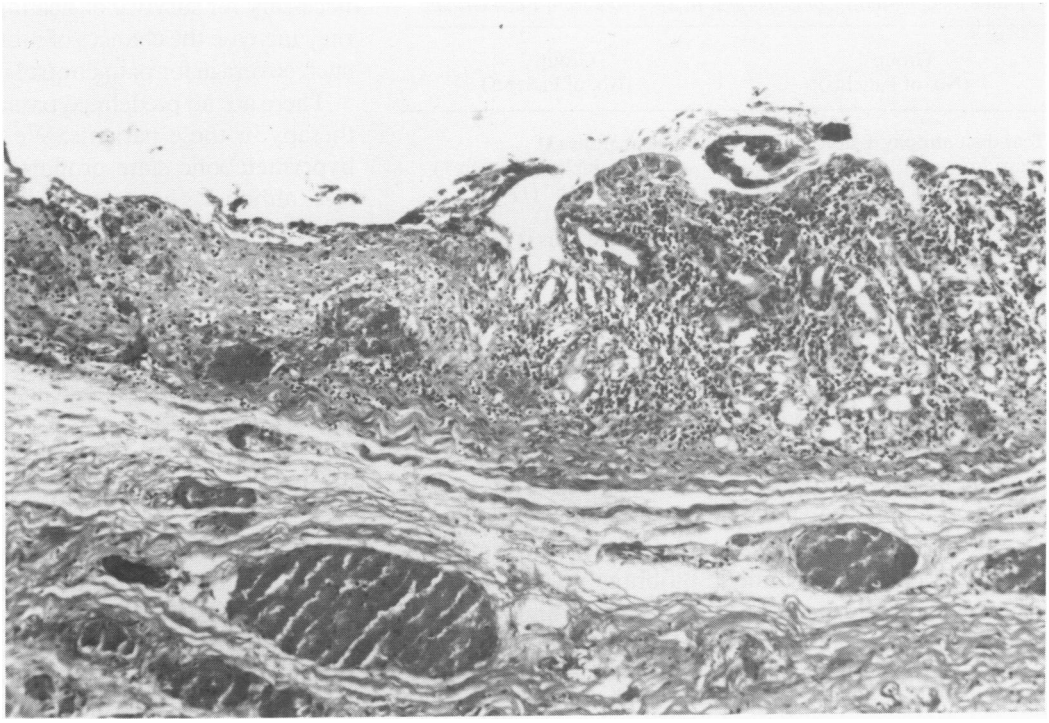

FIG. 3. Biopsy from the upper esophagus of a nonsurvivor from group 2, demonstrating the specificity of the mechanisms of slough for squamous epithelium. Islands of congenital ectopic gastric mucosa (columnar epithelium), to the right, are uninvolved, despite their location. The normal esophageal mucosa, on the left, has been denuded by complete loss of stratified squamous epithelium. Magnification ×32.

might increase the morbidity in these patients. In the absence of specific therapy for esophageal ulcerations discovered by endoscopy, such examinations have been reserved for symptomatic, clinically stable individuals. Esophagograms and upper GI roentgenograms are currently performed during the recovery phase of symptomatic survivors to screen for abnormalities. Stein described an esophageal stricture in a patient after a 75% skin slough.[20] An esophageal web in a group 2 survivor was disrupted during endoscopy, which also revealed resolving esophageal inflammation. Patients should be monitored for such complications by an esophagogram and appropriate endoscopy. Although we have not observed vaginal stenosis, it has been described after SJS[27] and merits attention during outpatient follow-up.

The lack of defects or slough in the tracheobronchial mucosa supports the concept that the lesion is specific for stratified squamous epithelium. This also suggests that the copious sputum and tracheobronchial casts that these patients occasionally cough up[12] originate in supraglottic pharyngeal mucosa or from secondary pneumonia.

Pulmonary emboli were discovered incidentally in nearly half of the patients who were autopsied. Thromboembolism has been described during the acute phase of erythema multiforme.[28] Such complications are more likely caused by prolonged bedrest than by the primary disease. The frequent occurrence of esophageal and pharyngeal mucosal defects distinguishes these patients from those with cutaneous burns. Consequently, intubation of the lungs or the stomach may be more complicated. Whenever possible, soft Silastic® tubes and gentle technique are indicated. Obstruction of maxillary and frontal sinus drainage by nasotracheal tubes is a potential complication that might be increased by the presence of necrotic tissue in these patients, leading to a sinus abscess. While this has not been documented, in our experience such documentation is difficult to obtain in the intensive care unit setting with a critically ill patient.

Topical therapy with 0.5% $AgNO_3$ is currently preferred for these patients. This agent allows control of cutaneous flora without sulfate exposure, and the gauze dressings protect the exposed dermis from further trauma. Hyponatremia and hypothermia may complicate $AgNO_3$ topically but have not been a major problem. Group 1 patients were covered with povidone iodine foam for the most part. In theory, the superficial nonescharotic lesion of the epidermis should not require topical chemotherapy; thus, this difference in topical therapy should not have significantly contributed to the improved survival observed in group 2. Topical chemotherapy may be more important in the patient with severe neutropenia.

Marvin described five patients managed with a nonsteroid protocol, which includes coverage of all TEN/SJS patients with porcine heterografts.[6] Demling combined porcine heterograft coverage with conventional steroid therapy in a single patient.[3] In contrast, Davidson achieved

TABLE 7. *Long-term Complications in Survivors from Each Group**

Group 1 (No. of Patients)	Group 2 (No. of Patients)
Tear duct atrophy + sicca syndrome (3)	Symblepharons (2) (ankylosymblepharons in 1)
Gastric ulcer (1)	Esophageal "web" (1)
Sigmoid colon phlegmon (1)	Perianal abscess (1)
	Hypertrophic scars (1)
	Sicca syndrome (1)

* Some patients had more than one complication.

adherence with homograft but not pigskin in a steroid-treated patient.[2] It is possible that concomitant steroid therapy interferes with the adhesion of these skin substitutes to the underlying wound. Four patients from group 2 underwent secondary coverage—one with homograft and the rest with the synthetic Biobrane®. There were no problems with adherence of these biologic and synthetic skin substitutes, which decreased the pain and protected the cutaneous wound until healing. The rate and quality of healing seemed no better than that observed under 0.5% $AgNO_3$ dressings. The extensive debridement required for proper placement is extremely painful and requires general anesthesia. Ketamine has been used in all such procedures without complication. In complicated patients, such anesthesia is most safely accompanied by endotracheal intubation. As mentioned earlier, such instrumentation may pose problems for these patients. Our experience suggests that synthetic or biologic skin substitutes are not necessary for survival or healing. Concern that anesthesia may increase the chances of morbidity has led us to reserve such coverage for pain control in uncomplicated patients.

There are no predefined parameters to guide nutritional therapy in these patients. We have chosen to assume a hypermetabolic state proportional to the extent of skin loss, although there are no studies to support or refute this. Increased evaporative water losses, resulting from the loss of stratum corneum, contribute to an increased metabolic rate.[29] Epidermal slough increases nitrogen losses acutely as well.[30] Metabolic studies are clearly indicated but may be altered by previous steroid therapy and the acute deficits that usually develop immediately before transfer.

A recent exposure to drugs was implicated as the "cause" of TEN/SJS in every patient from both groups. In many cases, the exposure was minor (for example, a single oral dose of erythromycin followed by 95% TBSA slough) or unlikely (for example, two patients, one from each group, had the onset of skin involvement while receiving methylprednisolone pulse therapy, 1 g daily, for the manifestations of systemic lupus erythematosus). Eight of the 30 had symptoms compatible with a viral upper respiratory infection before drug exposure. A ninth patient, previously treated with ampicillin and Dilantin developed diagnostic elevations of antibody titers for Epstein–Barr virus (acute 1:40, convalescent 1:1280). A tenth patient, previously treated with trimethoprim-sulfamethoxazole for pneumocystis pneumoniae, had cytomegalovirus cultured from the urine. This patient was also suffering from the acquired immunodeficiency syndrome (AIDS), which is caused by a retrovirus. Active viral infections may produce a temporary sensitization to certain drugs, as suggested by Kauppinen.[31] TEN/SJS has been reported in combination with a number of other diseases, including infectious mononucleosis.[9,21,32,33] Ampicillin therapy of patients suffering from infectious mononucleosis was reported to cause a diffuse rash, although severe epidermal slough was absent.[19] Acute viral infections and active autoimmune diseases may result in an antigen–antibody ratio favoring the formation of immune complexes. Such immune complexes have been described in the very early stages of SJS, but they are not found later during slough.[34,35] It is not clear whether immune complexes are a cause or effect of the primary disorder.

The most severe long-term complication (Table 7) in group 2 patients occurred in the patient described earlier who had disseminated methicillin-resistant sepsis due to a suppurative thrombophlebitis. This same organism colonized and destroyed the conjunctiva, leading to scarring, ankylosymblepharon (complete fusion of the lid to the globe), and blindness (Fig. 4). The patient is currently

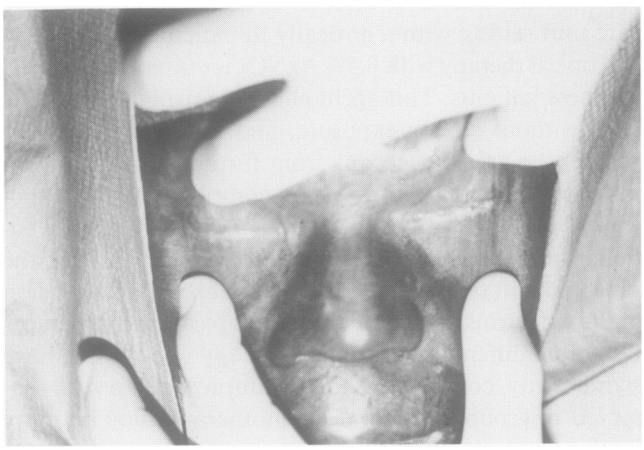

FIG. 4. Ankylosymblepharon formation in a survivor from group 2 whose clinical course is described in the text. There is complete obliteration of the conjunctival spaces by scar formation, with fusion of the lid to the globe. This patient has undergone buccal mucosal grafting to recreate the conjunctival space in preparation for corneal replacement.

undergoing staged reconstruction of the conjunctival mucosa with buccal mucosal grafts. Mild symblepharon formation occurred in another patient but has not presented significant problems. A third patient developed a perianal abscess soon after discharge, which required incision and drainage. Other complications in this group were of a more cosmetic nature similar to those observed in the earlier steroid-treated patients. The increased incidence of severe complications in group 2 patients more likely resulted from the greater salvage of severely injured patients rather than the omission of corticosteroids, although the latter has not been excluded.

Our total of 30 patients with biopsy proven TEN/SJS is one of the largest single center experiences reported in the literature and the only one that attempts to compare steroid and nonsteroid management of equal numbers of patients. It may be argued that blinded or randomized trials of these drugs are necessary before such conclusions can be reached. Given the infrequent and unpredictable occurrence of these disorders, along with the tertiary role of most burn centers caring for these patients, a blinded or randomized trial would require earlier transfer and initial nonsteroid management by referring institutions. It is important to note that corticosteroid therapy has been advocated with no supporting randomized or blinded studies. Despite the use of historical controls, our experience raises serious ethical concerns about the administration of high-dose corticosteroids to these patients under any circumstances, since it appears that the use of these potent immunosuppressive drugs is associated with increased mortality.

The current studies do not allow specific criticism of the use of these drugs before burn center admission or for patients with minor forms of these diseases. Since steroid therapy did not prevent progression of skin loss in group 1 and, by comparison, abrupt cessation of steroids was not associated with an increased incidence of skin loss or exacerbation of TEN/SJS in group 2, it is hard to believe that these drugs produce anything more than symptomatic improvement in minor forms of the disease and may increase morbidity.[22] Vitamin A (20,000 U intramuscularly daily) has been given to recent patients, while steroids have been tapered, to augment immunocompetence and promote re-epithelialization.[36] Previous authors have avoided vitamin A therapy for fear of negating the therapeutic immunosuppressive effects of steroids.[3] We have noted no such adverse effects, lending further support to the concept that immunosuppressive corticosteroid therapy does not prevent progression of the disease. Such therapy usually complicates the later management and makes difficult the initial assessment of patients transferred to the burn center. Referring institutions are encouraged to withhold corticosteroids and transfer the patient as soon as possible.

Further improvement in survival will require a greater understanding of the pathophysiology of the primary disease without the artifacts introduced by high-dose corticosteroid therapy. Our experience suggests that management of these patients without immunosuppressive therapy but with appropriate support and diligent monitoring will result in improved survival and is certainly indicated for those severely injured patients who require care in a burn center.

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