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Genitourinary involvement and management in children with Stevens–Johnson syndrome and toxic epidermal necrolysis

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Summary

Background
Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are devastating hypersensitivity disorders that cause epidermal cell death and can affect all epidermal surfaces, including the urethra, vagina, labial and scrotal skin. Despite the well-described ocular and orofacial manifestations of SJS/TEN, there is a paucity of reports on the genitourinary (GU) symptoms and their management. Specifically, consulting services often ask the pediatric urology team if it is safe to place a urethral catheter, but there is no data in the literature to help guide management. The present study sought to review all pediatric cases of SJS/TEN in a tertiary care hospital to determine the incidence and optimal management of GU manifestations, including the use of urethral catheters.

Methods
With IRB approval, cases of SJS and TEN that were managed as an inpatient between January 2008 and June 2015 were retrospectively reviewed in order to identify the extent of GU involvement/manifestations, the treatment provided, use of urethral catheterization and long-term follow-up or complications.

Results
Thirty-one patients (15 female, 16 male; age range 2–18 years) presented with SJS or TEN over the study period. Etiologies for SJS/TEN included mycoplasma infection (48%) and medications (45%). Incidences of GU manifestations at presentation and their management are shown in Summary Table. Overall, 74% of patients had genital involvement of skin lesions. In 12 cases (39%), urology consultation was obtained. Twenty patients (61%) complained of dysuria and one child had gross hematuria in the setting of meatal lesion. Petroleum jelly was used in the majority of patients. A urethral catheter was placed in eight patients (25.8%, four female, four male) with a range of duration of 7–23 days. No patient developed hematuria or any other complications (i.e. strictures or urinary symptoms) after catheter removal. One boy required lysis of penile adhesions in the short-term. One of each gender developed penile and labial adhesions on long-term follow-up that self-resolved.

Conclusions
GU involvement in SJS/TEN occurred in almost three-quarters of patients and was managed conservatively like other skin/mucosal manifestations. Long-term sequelae were rare and urethral catheterization appeared to be safe, without any short-term or long-term complications.

Summary Table Genitourinary manifestations and management of Stevens–Johnson syndrome and toxic epidermal necrolysis in children.

Variables[a]	Overall	Males	Females	*P*-value**
N	31	16	15	–
Age at presentation, years				0.62
Median (IQR)	10.9 (7.4–14.1)	10 (8–14)	13 (6.7–14.5)	
Etiology of SJS				0.68
Mycoplasma	15 (48.4)	9 (56.3)	6 (40.0)	
Lamotrigine	4 (12.9)	1 (6.3)	3 (20.0)	
Sulfamethoxazole/Trimethoprim	4 (12.9)	1 (6.3)	3 (20.0)	
Azithromycin	3 (9.7)	2 (12.5)	1 (6.7)	
Amoxicillin	2 (6.5)	1 (6.3)	1 (6.7)	
Valproic acid	1 (3.2)	1 (6.3)	0 (0)	
Recurrent SJS	1 (3.2)	0 (0)	1 (6.7)	
Unknown	1 (3.2)	1 (6.3)	0 (0)	
Signs/Symptoms				
Dysuria	20 (64.5)	10 (62.5)	10 (66.7)	1.00
Hematuria	1 (3.2)	1 (6.3)	0 (0)	1.00
Urinary retention	5 (16.1)	3 (18.8)	2 (13.3)	1.00
Scrotal/labial lesions	11 (35.5)	5 (31.3)	6 (40.0)	0.72
Penile/vulvar lesions	18 (58.0)	7 (43.8)	11 (73.3)	0.15
Meatal lesions	12 (38.7)	9 (56.3)	3 (20.0)	0.07
Acute kidney injury	1 (3.2)	1 (6.3)	0 (0)	1.00
Management				
Urology consult	12 (38.7)	7 (43.8)	5 (33.3)	0.72
Foley urethral catheter	8 (25.8)	4 (25.0)	4 (26.7)	1.00
Topical petroleum jelly	20 (64.5)	9 (56.3)	11 (73.3)	0.46
Phenazopyridine	3 (9.7)	3 (18.8)	0 (0)	0.23
Topical lidocaine	1 (3.2)	1 (6.3)	0 (0)	1.00
Surgery	1 (3.2)	1 (6.3)	0 (0)	0.49
Long-term complications				
Penile/labial adhesions	3 (9.7)	1 (6.3)	2 (13.3)	1.00

SJS = Stevens–Johnson syndrome; TEN = toxic epidermal necrolysis; IQR = interquartile range.
**P*-values compared males vs. females with Wilcoxon rank-sum test for age and Fisher's exact test for all other variables.
[a] Values shown are number (%) unless otherwise specified.

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Introduction

Stevens—Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, but potentially devastating, diseases of the skin and mucosal surfaces that affect two in every 1,000,000 patients annually [1]. Both conditions can affect adults as well as children, including newborns and infants [1]. SJS and TEN are immune-mediated diseases typically incited by exposure to drugs or infections. The clinical presentation includes: cutaneous target lesions, blisters, bullae, epidermal necrosis and hemorrhagic mucositis, and can affect extensive amounts of the epidermal surfaces of the body [1—4].

The clinical classification of SJS and TEN is based on how much total body surface area (BSA) is affected; thus, the diseases are on a continuous spectrum with each other. The term SJS is used if $<$10% of the BSA is affected, while the term TEN is used if $>$30% of BSA is affected. SJS/TEN overlap syndrome is used to describe patients with between 10 and 30% of affected BSA [3]. In addition, these diseases are often centered on mucosal surfaces, including the epithelium of the urethra and external genitalia [4]. From a molecular standpoint, SJS/TEN is a T-cell-mediated disease with T cells thought to be a major inducer of basal keratinocyte apoptosis, which leads to separation of the upper epithelial layers from the lower ones [5]. The keratinized stratified squamous epithelium of the external genitalia and both the non-keratinized stratified squamous and pseudostratified columnar epithelium of the urethra all contain basal keratinocytes and are at risk of involvement. Genital sequelae have been reported in the gynecology literature, with several case reports showing labial adhesions, development of vaginal adenosis, and even significant obstruction leading to hydrocolpos [2,6—8]. Erosive balanitis and phimosis have been reported to occur in males [9].

Despite these reports, there is a knowledge gap regarding the long-term sequelae of urethral and perimeatal involvement. Moreover, there are no adequate data about the risk or role for bladder catheterization in the acute management. It has been suggested that a urethral catheter may be used to prevent urethral strictures, although this must be balanced with the potential risk of infection [4]. On the other hand, there is an anecdotal belief that urethral catheter placement may potentiate urethral strictures or meatal stenosis, but this has never been demonstrated. Children with this disease are in significant pain, and often develop urinary retention due to a combination of the pain as well as the narcotics used to control their pain. Furthermore, children with severe oral mucosal involvement and lesions may require intubation for a period of time, and acute urinary retention may occur in this setting, necessitating the need for urethral catheterization. In general, urogenital lesions are managed with the same wound care as used for the rest of the body. However, the decision to place a urethral catheter requires careful consideration. At the present tertiary care center, the pediatric urology team is often consulted specifically with the question: "Is it safe to place a urethral catheter?" The paucity of information in the literature makes this question difficult to answer.

To help answer this question and further understand the genitourinary involvement in SJS/TEN, the present study sought to determine the incidence of urological involvement and complications from SJS/TEN in the pediatric population, and to assess how the management of genitourinary lesions affects long-term outcomes in these children. It also wanted to determine if outcomes differed based on gender. It was hypothesized that the use of urethral catheterization would not cause any increase in adverse events when compared with patients who did not require catheterization, and that if complications did occur, they would likely affect boys more than girls.

Materials and methods

An institutional review board-approved retrospective cohort study of pediatric SJS/TEN cases that presented to the present tertiary care center between January 2008 and June 2015. The cohort was constructed from dermatology consultation records, in order to capture all cases of SJS/TEN. Hospital policy is to consult dermatology for any suspected case of SJS/TEN. No patients were excluded.

The primary outcome measure was incident urologic sequelae, which was abstracted from review of dermatology, urology, and primary care charts during both the acute hospitalization and follow-up. Signs or symptoms of impaired flow, split stream, or stranguria were used to define presence or absence of stricture disease. Covariates included age at presentation, gender, disease etiology, length of hospitalization, whether or not urology was consulted, what type of treatment was used for urogenital lesions, use and duration of urethral catheterization, and any complications related to catheter use. Gender was used to stratify analysis, since it was suspected that the longer urethral length in males might predispose to more complications.

Descriptive statistics were used to assess overall cohort characteristics. The Wilcoxon rank-sum test and Fisher's exact test were used to compare continuous and categorical variables, respectively, between males and females. All analyses were performed with Stata (version 14.1, StataCorp, USA) with a two-tailed alpha of 0.05.

Results

A total of 31 patients with SJS or TEN were identified. Fifteen patients were female and 16 were male. Median age at time of presentation was 10.9 years (interquartile range (IQR) 7.4—14.1 years). Diagnosis of SJS or TEN was confirmed in all cases by the pediatric dermatology service (Fig. 1 and Fig. 2a and b). Individual case characteristics are shown in Table 1. In the vast majority of patients, the cause of SJS/TEN was either mycoplasma infection (48%) or medication (45%), including sulfamethoxazole/trimethoprim in 13% of all cases. Overall, 22 patients (71%) had involvement of the genitalia. On initial evaluation, 12 of the 31 patients (39%) were noted to have meatal/urethral involvement on exam, and 20 of 31 (65%) complained of dysuria. Eleven of the 15 females (73%) had labial or vulvar involvement. Five of the 16 males (31%) had scrotal

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