Letter

Research letter

Delayed admission to a specialist referral center for Stevens-Johnson syndrome and toxic epidermal necrolysis is associated with increased mortality: A retrospective cohort study

To the Editor: Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are rare, severe cutaneous adverse drug reactions. The average mortality across the spectrum is 25%.[1] Guidelines recommend that such cases be managed in reference centers.[2] Our study aims to evaluate the impact of delayed admission to an SJS/TEN referral center on clinical outcomes.

A retrospective cohort study was conducted from 2005 to 2018 at the Singapore General Hospital (SGH), the national referral center for SJS/TEN. Outcomes of interest included mortality, the incidence of bacteremia at SGH, ICU admission, and length of hospital stay.

Admissions occurring within 4 days of skin blistering according to clinical records were considered early admissions and delayed admissions were defined as admissions occurring 5 days or more after skin blistering. The consensus of the 5-day cut-off was based on 1) a multi-center study in Europe,[1] wherein the median admission delay was 5-7 days across several centers and 2) the natural history of SJS/TEN, where the disease evolves from initial blistering to hospitalization in 3 days, then progresses to maximum detachment in another 5 days.[3]

A total of 123 patients with SJS/TEN were included in this study. There were 93 (76%) patients with early admissions and 30 (24%) with delayed admissions. Baseline characteristics are shown in Table I.

Univariate analyses demonstrated a significant difference in outcomes between early and late admission patients for mortality (14% vs 37%; $P = .007$), incidence of bacteremia (20% vs 52%; $P = .001$), rate of ICU admission (14% vs 41%; $P = .002$), and total length of stay at SGH (16 ± 22 vs 28 ± 23; $P = .01$). A dose-response relationship was demonstrated between mortality and admission delay, with mortality increasing from 15% in those admitted within 0-3 days, to 19% in those admitted within 4-5 days, and to 33% in those admitted within 6 days.

A logistic regression model adjusting for disease classification and transfer status showed similar outcomes after adjustment (predictors SCORTEN and ABCD-10 were collinear with disease classification and excluded from the final model) (Table II). Similar findings were seen during a secondary analysis of patients directly admitted to SGH from the community (n = 66), suggesting that these differences in outcomes were unlikely to be influenced by transfer status.

Our findings suggest that early admission to reference centers is associated with better outcomes. Early admission and management may mitigate acute metabolic and septic complications; allow for early identification and withdrawal of culprit medications, which improves outcomes[4]; and permits earlier initiation of immunomodulatory therapy which is most effective during the progressive phase of the disease. Additionally, outcomes have been shown to be superior in centers with higher volumes of SJS/TEN cases.[5] Limitations, including referral bias, potential confounders of transfer status and disease classification must be acknowledged. However, we adjusted for these in our multi-variate model and a separate analysis was performed, limiting the data to nontransfer cases, which yielded similar outcomes.

Establishing a network of reference centers has been advocated.[5] Our findings provide contemporary evidence supporting the expeditious transfer and management of cases in reference centers.

Abigail E. Clark, BS,[a] Stephanie Fook-Chong, MSc,[b] Karen Choo, MRCP,[b] Choon Chiat Oh, FRCP,[b,c] Yi Wei Yeo, MMed,[b,c] Shiu Ming Pang, FRCP,[b] and Haur Yueh Lee, MRCP[b,c]

From the Duke University School of Medicine, Durham, North California,[a] Singapore General Hospital, Singapore,[b] and Duke-National University of Singapore Medical School, Singapore.[c]

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Correspondence to: Haur Yueh Lee, MRCP, 20 College Road, Singapore 169856

E-mail: lee.haur.yueh@singhealth.com.sg

Table I. Clinical characteristics for all SJS/TEN patients

Clinical characteristics	All (n = 123)	Early admission (n = 93)	Late admission (n = 30)	*P* value
Male	47 (38%)	35 (38%)	12 (41%)	.72
Age (years)	56 (19)	53 (19)	67 (20)	.11
Ethnicity				.30
Chinese	81 (66%)	58 (63%)	23 (77%)	
Malay	29 (24%)	25 (27%)	4 (13%)	
Other	13 (11%)	10 (11%)	3 (10%)	
Disease				.066
SJS	45 (37%)	39 (42%)	6 (20%)	
SJS/TEN	41 (33%)	30 (32%)	11 (37%)	
TEN	37 (30%)	24 (26%)	13 (43%)	
Maximum % BSA involved	23 (22)	20 (19)	33 (27)	**.016**
SCORTEN	2.1 (1.2)	2.0 (1.2)	2.6 (1.2)	**.013**
ABCD-10	2.0 (1.4)	1.9 (1.5)	2.2 (1.2)	.14
Transfer*	57 (46%)	36 (39%)	21 (70%)	**.003**
Inciting Drug				.47
Penicillin/cephalosporin antibiotic	7 (6%)	5 (5%)	2 (7%)	
Other antibiotic	8 (7%)	5 (5%)	3 (10%)	
Sulfonamides	10 (8%)	6 (7%)	4 (13%)	
Allopurinol	19 (15%)	15 (16%)	4 (13%)	
Anticonvulsants	27 (22%)	24 (26%)	3 (10%)	
NSAID	5 (4%)	5 (5%)	0 (0%)	
Trimethoprim-sulfamethoxazole	2 (2%)	1 (1%)	1 (3%)	
Other drug	27 (22%)	18 (19%)	9 (30%)	
Unknown drug	1 (0.8%)	1 (1%)	0 (0%)	
SJS/TEN not caused by drug	17 (14%)	13 (14%)	4 (13%)	
Comorbidities				
Malignancy	18 (145%)	13 (14%)	5 (17%)	.72
Liver disease	4 (3%)	3 (3%)	1 (3%)	.98
Renal disease	17 (14%)	13 (14%)	4 (13%)	.93
AIDS	4 (3%)	3 (3%)	1 (3%)	.98
Cardiac disease	25 (20%)	14 (15%)	11 (37%)	**.011**
Diabetes mellitus	19 (15%)	15 (16%)	4 (13%)	.71
Autoimmune/connective tissue disease	11 (9%)	8 (9%)	3 (10%)	.82
Charlson Comorbidity Index	2.70 (2.69)	2.57 (2.72)	3.10 (2.63)	.28

Data are presented as count (%) or mean (SD). Bold values are statistically significant.
NSAID, Non-steroidal anti-inflammatory drug.
*Indicates the number of patients transferred to Singapore General Hospital.

Table II. Effect of admission delay on clinical outcomes adjusted for disease classification and transfer status

Outcome	Effect of admission delay	*P* value	Effect of disease classification*	*P* value	Effect of transfer	*P* value
Mortality	2.9 (1.0, 8.3)	**.05**	3.4 (1.6, 7.1)	**.001**	0.64 (0.2, 1.9)	.44
Bacteremia	3.7 (1.2, 11.2)	**.02**	6.6 (2.9, 15.1)	**<.0001**	11 (0.4, 3.4)	.843
ICU admission	3.3 (1.1, 9.8)	**.03**	5.8 (2.4, 13.9)	**<.0001**	0.9 (0.3, 2.9)	.85
Length of stay	6.9 (-3.8, 17.7)	.20	11.7 (6.1, 17.2)	**<.0001**	-0.3 (-9.7, 9.2)	.96

For length of stay outcome, beta coefficient (95% CI) is reported, all other outcomes are reported as OR (95% CI). Only survivors are included in the analysis for length of hospital stay. Bold values are statistically significant.
*The reference category was Overlap and TEN for the reporting of OR or Beta coefficient.

Conflicts of interest

None disclosed.

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