Poor reporting and documentation in drug-associated Steven Johnson Syndrome and Toxic Epidermal Necrolysis – Lessons for medication safety

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Running title: SJS & TEN – Epidemiology, reporting and medication safety

Keywords: Severe cutaneous adverse drug reactions, antibiotic allergy, T-cell mediated hypersensitivity, adverse drug reactions

Conflicts of interest: There are no conflicts to declare for any of the included authors.

Words: 790 (including references)

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bcp.13103

Dear Editor,

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are associated with significant morbidity and mortality, therefore assigning drug-causality is central to preventing reoccurrence[1]. Graudins *et al*. recently demonstrated deficiencies in the long-term labelling of patients with severe cutaneous adverse drug reactions (cADR). This has significant ramifications, as a single prescribing error in a patient with a history of SJS or TEN has the potential to cause serious morbidity and mortality, especially when commonly employed antibiotics are implicated in up to 50% of cADR [2]. What remains unknown is if ADR reporting in SJS and TEN is a widespread problem, and if such ADR reports are also conveyed to primary care physicians.

We write to share own experience with SJS and TEN over a 10-year period. The aim was to examine the aetiology of antibiotic associated SJS and TEN (AA-SJS/TEN) in terms of drug causality, clinical characteristics, treatment and patient outcomes, subsequent ADR reporting and documentation, compared with non-antibiotic associated SJS and TEN (NA-SJS/TEN).

We performed a retrospective observational cohort study and identified twenty-six cases of SJS and TEN via International Statistical Classification of Diseases and Related Health Problems (ICD-10) coding, for the period 1st of January 2004 to 31st of December 2015 at Austin Health (Victoria, Australia). Baseline demographic, co-morbidity, drug causality assessments (algorithm for assessment of drug causality [ALDEN][3]), clinical characteristics, treatment/outcomes, ADR committee record, electronic medical record (EMR) and outpatient (primary care) allergy records were collated for each patient.

The median age of the cohort was 41.5 (IQR 25-52), median ALDEN score 5 (5= probable, IQR 4-6) and 62% (16/26) male. Forty-two per cent (11/26) were AA-SJS/TEN and 58% (15/26) NA-SJS/TEN). When comparing NA-SJS/TEN and AA-SJS/TEN, a higher ALDEN score (5[probable] vs. 4[possible], p=0.004) and longer drug latency (median; 21-days vs. 5-days,

p=0.01) were noted in NA-SJS/TEN patients (**Supplementary Table 1)**. Seventeen antibiotics were implicated in the 11 cases of AA-SJS/TEN; aminopenicillins in 23%, sulphonamide antibiotics in 18% and glycopeptides in 12%. In NA-SJS/TEN, 46% were secondary to anticonvulsants, 20% to immunosuppressive medications (methotrexate and lefunomide) and single cases to risperidone and oxybutynin were noted.

Subsequent reporting and documentation of implicated drugs in SJS and TEN cases is demonstrated in **Figure 1**. Compared with Graudins *et al*. even fewer cases were referred to the ADR committee (50% vs. 72%) and not all implicated drugs were noted in the discharge summary (58% vs. 84%). Only 27% of patients had all implicated drugs noted in the outpatient (primary care) record, higher for AA-SJS/TEN than NA-SJS/TEN (55% vs. 7%, *p*=0.02). For NA-SJS/TEN a larger proportion of implicated drugs were noted in the discharge summary than in the outpatient record (53% vs. 7%, *p*=0.01). Two AA-SJS/TEN patients were given the same or class-related antibiotic post discharge, without reported adverse event.

Poor documentation of serious ADRs in the EMR and discharge summary is concerning, considering these form potentially the only communication to hospital clinicians and primary care physicians respectively. In cases of SJS and TEN, where mortality for antibiotic associated SCAR has been quoted at 25%[2], erroneous antibiotic prescriptions using the implicated antibiotic could have dire consequences, although the absence of cross-reactivity in T-cell mediated hypersensitivity for some beta-lactams and sulphonamides has been noted[4, 5]. This is noteworthy as antibiotics remain the causative drug in almost 50% of SJS and TEN cases, with commonly employed antibiotics such as aminopenicillins, sulphonamides and glycopeptides predominating. We focus on AA-SJS/TEN, as antimicrobials are frequently prescribed in hospital and community settings post ADR. Our study in addition to that by Trubiano *et al*. demonstrates that AA-SJS/TEN potentially presents more acutely than NA-SJS/TEN, reflected by the significantly shorter drug latency [2].

There are a number of limitations to this study, including the retrospective nature, small study numbers and potential for patients to have changed primary care providers post discharge. Nonetheless, it highlights that commonly employed antibiotics are often implicated in the acute onset of SJS and TEN, and further supports claims by Graudins *et al.* and others for the need to address recording of serious ADRs, especially antibiotics, to ensure medication safety [6]. Overall, greater vigilance is required to engage physicians and pharmacists to report to the ADR committee, ensuring accuracy of allergy documentation in the EMR and that appropriate information is conveyed to both patients and primary care physicians.

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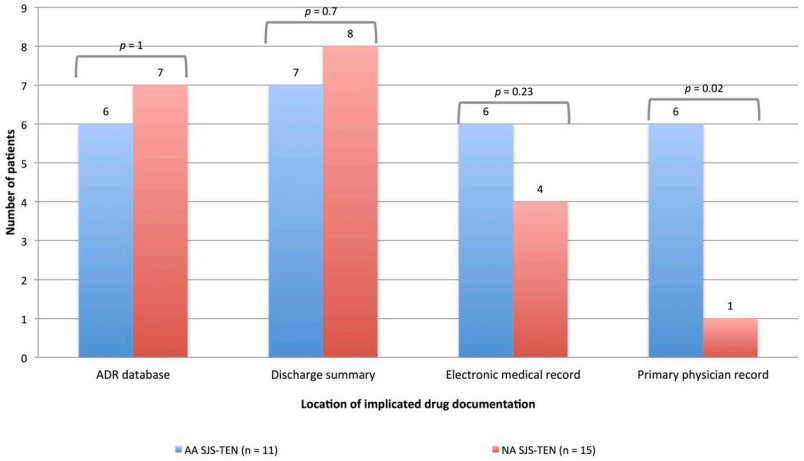
Figure 1 Legend: Documentation of implicated drugs in cases of SJS and TEN across multiple platforms

Abbreviations: AA, antibiotic associated; NA, non-antibiotic associated; SJS, Stevens-Johnson Syndrome; TEN, toxic epidermal necrolysis.

Table of Links

LIGANDS	
Adiponectin	IBMX
cAMP	IL-6
Dexamethasone	Indomethacin
Exenatide (exendin-4)	Insulin
Exendin (9-39)	Liraglutide
GLP-1	Metformin
TARGETS	
Other protein targets[a]	**Enzymes**[e]
FABP4	Acetyl CoA carboxylase
TNF-α	Adenylate cyclase
GPCRs[b]	Akt (PKB)
GLP-1 receptor	ERK1
Nuclear hormone receptors[c]	ERK2
PPARγ	FASN
Transporters[d]	Hormone sensitive lipase (HSL)
GLUT4	PKA

These Tables of Links list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan et al., 2016), and are permanently archived in The Concise Guide to PHARMACOLOGY 2015/16 ([a,b,c,d,e]Alexander et al., 2015a,b,c,d,e).*



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