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The Australasian Registry for Severe Cutaneous Adverse Reactions (AUS-SCAR) – Providing a roadmap for closing the diagnostic, patient, and healthcare gaps for a group of rare drug eruptions

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ABSTRACT

Background: Severe cutaneous adverse reactions (SCAR) are a group of delayed presumed T-cell mediated hypersensitivities associated with significant morbidity and mortality. Despite their shared global healthcare burden and impact, the clinical phenotypes, genomic predisposition, drug causality, and treatment outcomes may vary. We describe the establishment and results from the first Australasian registry for SCAR (AUS-SCAR), that via a collaborative network advances strategies for the prevention, diagnosis and treatment of SCAR.

Methods: Prospective multi-center registry of SCAR in Australian adult and adolescents, with planned regional expansion. The registry collects externally verified phenotypic data drug

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causality, therapeutics and long-term patient outcomes. In addition, biorepository specimens and DNA are collected at participating sites.

Results: we report on the first 100 patients enrolled in the AUS-SCAR database. DRESS (50%) is the most predominant phenotype followed by SJS/TEN (39%) and AGEP (10%), with median age of 52 years old (IQR 37.5, 66) with 1:1 male-to-female ratio. The median latency for all implicated drugs is highly variable but similar for DRESS (median 15 days IQR 5,25) and SJS/TEN (median 21 days, IQR 7,27), while lowest for AGEP (median 2.5 days, IQR 1,8). Antibiotics (54.5%) are more commonly listed as primary implicated drug compare with non-antibiotics agent (45.5%). Mortality rate at 90 days was highest in SJS/TEN at 23.1%, followed by DRESS (4%) and AGEP (0%).

Conclusion: In the first prospective national phenotypic and biorepository of SCAR in the southern hemisphere we demonstrate notable differences to other reported registries; including DRESS-predominant phenotype, varied antibiotic causality and low overall mortality rate. This study also highlights the lack of standardised preventative pharmacogenomic measures and *in vitro/in vivo* diagnostic strategies to ascertain drug causality.

Trial registration: ANZCTR ACTRN12619000241134. Registered 19 February 2019.

Keywords: Delayed hypersensitivity, T-cell mediated hypersensitivity, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Acute generalized exanthematous pustulosis, Drug reaction with eosinophilia and systemic symptoms, DRESS

INTRODUCTION

Severe cutaneous adverse reactions (SCAR), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and generalized bullous fixed drug eruption (GBFDE) are a group of heterogenous T-cell mediated hypersensitivity reactions[1,2] associated with considerable morbidity and mortality.[3] At present, there remain several healthcare gaps related to SCAR that might be bridged by multidisciplinary networks.[4,5]

The pathogenesis of SCAR and other delayed drug hypersensitivities is an aberrant T-cell response, typically to a small molecule medication in a susceptible individual. Patients may be at risk due to an underlying genetic predisposition,[6] as one of many important increasingly identified co-factors that result in disease onset. The best recognised drug-HLA association is HLA-B*57:01 and the abacavir hypersensitivity syndrome that resulted in the implementation of a global pre-prescription screening strategy since 2008.[7] Other SCAR-HLA associations include allopurinol DRESS/SJS/TEN (HLA-B*58:01),[8] carbamazepine SJS/TEN (HLA-B*15:02)[9] and vancomycin DRESS (HLA-A*32:01).[10] The understanding of these associations has led to cost-effective screening programs in some settings. However, there is a need to understand the incomplete positive and negative predictive values of HLA testing for medication-associated SCAR that impact clinical translation and knowledge of mechanisms.

Different forms of SCAR differ considerably in their clinical presentation, drug causality and the sensitivity of applied diagnostics.[11-13] A standardized global approach to determine the causative drug by *in vivo* skin testing after recovery from SCAR and safe prescribing (recommendations as to which drugs to avoid or are safe to use) remains absent. At present, there is an inability to easily ascertain drug causality by current *in vivo* (eg, skin testing) approaches and this is highly dependent on both the phenotype and culprit drug.[14,15] *Ex vivo/in vitro* immune diagnostics (eg, functional T-cell assays) are not universally available or standardized and remain primarily a research exercise rather than a clinical tool,[13,16] hence highlighting a current diagnostic gap in SCAR.[14]

Healthcare and treatment outcomes have been evaluated in other SCAR registries such as RegiS-CAR in Europe[17] and the RACGRAD study in Latin America.[18] A registry acting as a repository for the collection of epidemiological, clinical, phenotypic and biological samples has not been previously established in Australasia. Further, there are no established SCAR standards of clinical care or national guidelines. Therefore, the establishment of a local clinical registry for SCAR forms a crucial platform to help identify and close the management gaps that currently exist.

In 2019, the Australasian Registry of Severe Cutaneous Adverse Reactions (AUS-SCAR)[19] was established to capture SCAR in the inpatient Australian setting with planned regional expansion, to better define the morbidity and mortality from SCAR, and inform translational research to improve the prevention, diagnosis and management of patients with SCAR. The primary aim of AUS-SCAR is to ensure continued surveillance of new and emerging causative drugs and improvement pharmacovigilance. Further, secondary objectives include defining the epidemiology, host and drug factors that predict treatment outcomes, pharmacogenomic associations and long-term outcomes, including quality of life (QOL) impact. In this initial report we report on the clinical characteristics, including implicated demographics, implicated drug and clinical phenotype of the first 100 patients recruited to the first 14 sites in AUS-SCAR.

METHODS

Sites and study participants

AUS-SCAR (ACTRN No. 12619000241134) was established and is hosted by the Centre for Antibiotic Allergy and Research, Austin Health, Melbourne, Australia. The project was reviewed and approved by the Austin Health Human Research Ethics Committee (Reference: HREC/50791/Austin-2019). The protocol for AUS-SCAR was published in 2022.[19] Fourteen tertiary referral hospitals from states or territories around Australia have contributed to the registry to date (Supplementary Table 1). In brief, all participating sites are adult tertiary referral centres, 4 of which included designated regional burns referral centres. The burns centres in these regions

manage all cases of SJS, TEN, and SJS/TEN overlap due to the extensive skin loss and surgical management required.

Registry structure, data collection and biospecimens

The AUS-SCAR registry components, data collection, biospecimen recovery model and governance was previously published.[19] In brief, AUS-SCAR is overseen by a steering committee chaired by an investigator not associated with a clinical site, with broad multidisciplinary representation. At a patient level, following informed written consent from the participant or medical decision maker (MDM) (if applicable), prospective demographic, phenotypic, causality, treatment and outcome data were collected, as was saliva for DNA isolation.[19] A waiver of consent was approved for retrospective case inclusion for patients who died prior to obtaining consent. A 12-month quality of life (QOL) survey using a validated drug allergy questionnaire was also undertaken. At selected participating sites with sample collection capacity, additional biological samples were collected including peripheral blood mononuclear cells (PBMCs), skin tissue, blister fluid, and paraffin embedded sections. Blister fluid and PBMCs were utilised for *ex vivo* diagnostics as per previously published methods.[19-21]

Case definitions and validation

Cases were considered eligible for inclusion if the phenotype was consistent with published definitions,[19] agreed upon by 2 participating site investigators, and adjudicated by a dermatologist or immunologist, or proven on biopsy.[19] Skin biopsy definitions utilised are provided in Supplementary Methods. Following recruitment, case summaries were reviewed by the Centre for Antibiotic Allergy and Research Staff and presented to 2 independent investigators for external validation and final inclusion into the registry (See Supplementary Figure 1 for case summary example). If available skin testing concentrations deployed are detailed in Supplementary Methods.

Analysis and statistical methods

Statistical analysis was performed using Stata version 17.0 (StataCorp LLC, College Station, TX,

	Overall (n = 100)[a]	DRESS (n = 50)	SJS/TEN (n = 39)	AGEP (n = 10)
Participating site region/state				
Victoria	82 (82%)	40 (80%)	34 (87%)	7 (70%)
New South Wales	9 (9%)	4 (8%)	2 (5%)	3 (30%)
South Australia	6 (6%)	3 (6%)	3 (8%)	0 (0%)
Northern Territory	3 (3%)	3 (6%)	0 (0%)	0 (0%)
Sex (n, % female)	50 (50%)	22 (44%)	23 (59%)	4 (40%)
Age (years), median (IQR)	52 (37.5, 66)	49 (36, 63)	58 (43, 69)	47 (33, 62)
Ethnicity				
Oceanian (including Australian and New Zealand)	5 (5%)	2 (4%)	3 (8%)	0 (0%)
Australian Aboriginal	3 (3%)	2 (4%)	1 (3%)	0 (0%)
Melanesian and Papuan	1 (1%)	0 (0%)	1 (3%)	0 (0%)
Polynesian	1 (1%)	0 (0%)	1 (3%)	0 (0%)
North-West European	34 (34%)	16 (32%)	15 (38%)	3 (30%)
Southern and Eastern European	10 (10%)	7 (14%)	2 (5%)	1 (10%)
European unknown (Caucasian)	18 (18%)	9 (18%)	5 (13%)	4 (40%)
North African and Middle Eastern	2 (2%)	1 (2%)	1 (3%)	0 (0%)
South-east Asian	11 (11%)	4 (8%)	5 (13%)	2 (20%)
North-east Asian	5 (5%)	2 (4%)	2 (5%)	0 (0%)
Southern and Central Asian	12 (12%)	7 (14%)	5 (13%)	0 (0%)
American (north, central, south)	3 (3%)	2 (4%)	1 (3%)	0 (0%)
Sub-Saharan Africa	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Admitting Ward				
General medical	52 (52%)	32 (64%)	13 (33%)	6 (60%)
General surgical	7 (7%)	5 (10%)	1 (3%)	1 (10%)
Emergency	3 (3%)	1 (2%)	1 (3%)	1 (10%)
Intensive Care Unit	13 (13%)	3 (6%)	9 (23%)	1 (10%)
Burn unit	10 (10%)	0 (0%)	10 (26%)	0 (0%)
Other[b]	15 (15%)	9 (18%)	5 (13%)	1 (10%)
ICU admit during admission for SCAR	28 (28%)	10 (20%)	17 (44%)	1 (10%)
Burn unit required during admission	18 (18%)	1 (2%)	17 (44%)	0 (0%)
Any prior immune-mediated drug allergy	21 (21%)	9 (18%)	9 (23%)	2 (20%)
Prior immune-mediated non-antibiotic drug allergy	11 (11%)	6 (12%)	4 (10%)	0 (0%)
Type of prior non-antibiotic allergy				
Aspirin/NSAID/paracetamol	3 (3%)	0 (0%)	2 (5%)	0 (0%)
Antiepileptic	1 (1%)	1 (2%)	0 (0%)	0 (0%)
Other[c]	7 (7%)	5 (10%)	2 (5%)	0 (0%)
Prior immune-mediated antibiotic allergy	19 (19%)	8 (16%)	8 (21%)	2 (20%)
Number of different immune-mediated antibiotic allergies				
Single	14 (14%)	6 (12%)	6 (15%)	1 (10%)
Multiple	4 (4%)	1 (2%)	2 (5%)	1 (10%)
N/A	82 (82%)	43 (86%)	31 (79%)	8 (80%)

	Overall (n = 100)[a]	DRESS (n = 50)	SJS/TEN (n = 39)	AGEP (n = 10)
Type of prior immune-mediated antibiotic allergy				
Penicillin allergy	13 (13%)	6 (12%)	6 (15%)	1 (10%)
Beta-lactam (non-penicillin) allergy	7 (7%)	3 (6%)	2 (5%)	1 (10%)
Sulfonamide allergy	3 (3%)	2 (4%)	1 (3%)	0 (0%)
Age adjusted CCI, median (IQR)	2 (0, 4.5)	2 (0, 4)	3 (0, 6)	1.5 (0, 3)
Immunocompromised[d]	38 (38%)	18 (36%)	17 (44%)	3 (30%)
Time in days from index rash to admission at participating site (median, IQR)	5.5 (3, 13) (n = 98)	8.5 (4, 17.5) (n = 48)	5 (3, 11)	3.5 (2, 5)
Resolution of rash <15 days	25 (25%)	11 (22%)	8 (21%)	6 (60%)

Table 1. (Continued) Patient characteristics, by phenotype *Abbreviations: AGEP, acute generalized exanthematous pustulosis; SJS, Stevens Johnson Syndrome; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms; ATSI, Aboriginal and Torres Strait Islanders; IQR, interquartile range; CCI, age-adjusted Charlson Comorbidity Index; NSAID, non-steroidal anti-inflammatory drug.* [a]*A single patient of GBFDE (generalized bullous fixed drug eruption) was included in the total cohort but data for the single case are not represented.* [b]*Antibiotic Allergy (n = 1), Critical Care Unit (CCU) (n = 1), Cardiology (n = 1), Hospital in the Home (HITH) (n = 1), Haematology (n = 4), Oncology (n = 3), Neurology (n = 1), Orthopaedic (n = 1).* [c]*Contrast (n = 1), contrast/tramadol (n = 1), contrast/arsenic (n = 1), olanzapine/quetiapine/hydroxychloroquine (n = 1), Jumper Jack ant (n = 1), lenalidomide (n = 1), perindopril/atorvastatin/rosuvastatin (n = 1).* [d]*Immunocompromised – Cancer or haematological malignancy, transplant recipient, autoimmune or inflammatory condition, HIV, splenectomy.*

USA). Continuous variables were summarized using median and interquartile range (IQR), and categorical variables were summarized using frequency and percentage. Groups were compared using Kruskal Wallis test (continuous variables) or Fisher's Exact test (categorical variables).

RESULTS

The first 100 patients were recruited from July 2019 to October 2022 across 12 of the 14 participating sites in Victoria (n = 7), New South Wales (n = 3), South Australia (n = 1), and the Northern Territory (n = 1). Patient characteristics are presented overall and stratified for phenotype in Table 1. Forty-five percent of patients had at least 1 biospecimen collected (blood, skin, or blister fluid) and 95% had DNA collected (Supplementary Table 2). The primary implicated drugs stratified for antibiotic and non-antibiotic, and specific class are demonstrated in Fig. 1. All implicated drugs are provided in Supplementary Figure 2. The median latency (time from drug commencement to rash onset) for all implicated drugs are highly variable but are similar for DRESS (median 15 days IQR 5,25) and SJS/TEN (median 21 days, IQR 7,27), while AGEP has lower latency (median 2.5 days, IQR 1,8). Further,

individual site investigator causality assessments and individual implicated drugs are shown in Supplementary Tables 3 and 4, respectively. Patients with DRESS comprised 50% of the cohort, 39% with SJS/TEN, and 10% with AGEP. The median age was 52 years (interquartile range, IQR, 37.5, 66.0) with 1:1 male-to-female ratio in the cohort. Patients with SJS/TEN were older with a median age of 58 years, compared to a median 49 years in DRESS and 47 years in AGEP. SJS/TEN patients were more likely to be female (59%), compared with AGEP (40%) and DRESS (44%). The median Charlson comorbidity index was 2 (IQR, 0,4.5.0) and 38% of the cohort was immunocompromised. A summary of Patient Comorbidities Charlson Comorbidity Index and Patient Comorbidities Immunocompromised Status are shown in Supplementary Table 5. Nineteen patients reported a previous skin disorder (Supplementary Table 6). Twenty-one percent of all patients had a label of one or more known prior medication allergies, 4% with a history of the same reaction to same drug (Supplementary Table 4). The median length of stay during the index admission at the participating site was 11 days (IQR, 6,29); this was highest in SJS/TEN patients at 14 days (IQR, 7,27). The median time from rash onset to hospital admission was 5.5 days
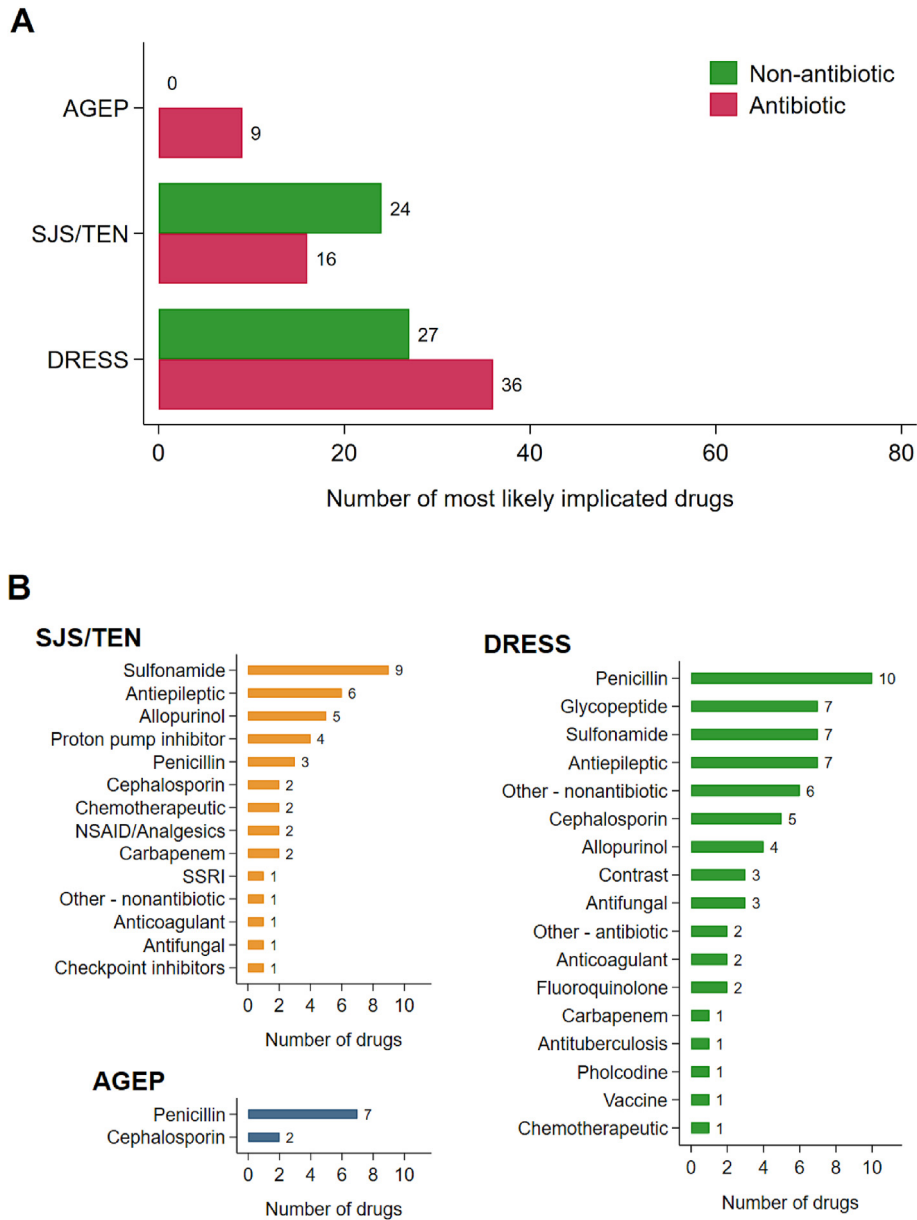
Fig. 1 Most likely implicated drug classes by phenotype A) Phenotypes stratified for primary implicated antibiotic vs non-antibiotic **B)** Phenotypes stratified for primary implicated drug class **Abbreviations**: PPI, proton-pump inhibitors; SSRI, selective serotine receptor inhibitors; NSAID, non-steroidal anti-inflammatory drug Other antibiotic: daptomycin, minocycline Other nonantibiotic: anastrozole, amiodarone, bortezomib Vaccines (n = 8): Comirnaty Pfizer (1), Hep B (1), Meningococcal Group B multicomponent (1), Meningococcal polysaccharide conjugate (1), pneumococcal (1)

(IQR, 3,13). Twenty-eight percent of all patients were admitted to an intensive care unit (ICU); this rate was highest in SJS/TEN patients (41%) (Supplementary Table 7).

Regarding key clinical characteristics, documented fever was most prevalent in DRESS cases (68%), compared with SJS/TEN (33.3%) and AGEP (4%). Mucosal involvement was a predominant sign in SJS/TEN (94.9%) but less frequently reported in DRESS (22%). Facial oedema was noted in 62% of DRESS and 43.6% of SJS/TEN patients. Eosinophilia was present in 86% of DRESS cases, it was also reported in 45.5% of AGEP patients. Rash resolution did not occur until at least 15 days post rash onset for most patients (70%). Internal organ involvement was noted in 54% of SJS/TEN, 86% of DRESS and 30% of AGEP cases. The median RegiSCAR

	Overall (n = 100)	DRESS (n = 50)	SJS/TEN (n = 39)	AGEP (n = 10)	p-value
Did the patient receive medical treatment (Corticosteroids [systemic/topical], antiviral)	95 (95%)	45 (90%)	39 (100%)	10 (100%)	0.097
Treatment or supportive care					
Systemic corticosteroids	77 (77%)	42 (84%)	29 (74%)	5 (50%)	0.066
Topical corticosteroids	79 (79%)	39 (78%)	30 (77%)	9 (90%)	0.82
Antivirals	8 (8%)	2 (4%)	6 (15%)	0 (0%)	0.14
Antibiotics	18 (18%)	8 (16%)	9 (23%)	1 (10%)	0.64
Paracetamol	37 (37%)	16 (32%)	19 (49%)	1 (10%)	0.052
NSAIDS	3 (3%)	1 (2%)	2 (5%)	0 (0%)	0.70
Intravenous immunoglobulin	18 (18%)	3 (6%)	15 (38%)	0 (0%)	<0.001
Plasma exchange	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Immunomodulatory therapy	15 (15%)	6 (12%)	9 (23%)	0 (0%)	0.15
Nasogastric feeding or TPN	12 (12%)	5 (10%)	6 (15%)	0 (0%)	0.47
Other[a]	17 (17%)	9 (18%)	7 (18%)	1 (10%)	1.00
Antiviral treatment					
Aciclovir (Intravenous)	6 (6%)	0 (0%)	6 (15%)	0 (0%)	0.007
Aciclovir (oral)	1 (1%)	0 (0%)	1 (3%)	0 (0%)	0.49
Valaciclovir	4 (4%)	2 (4%)	2 (5%)	0 (0%)	1.00
Immunomodulatory therapy					
Ciclosporin	3 (3%)	2 (4%)	1 (3%)	0 (0%)	1.00
Etanercept	9 (9%)	1 (2%)	8 (21%)	0 (0%)	0.011
Mepolizumab	3 (3%)	3 (6%)	0 (0%)	0 (0%)	0.46
Other[b]	2 (2%)	2 (4%)	0 (0%)	0 (0%)	0.60
Supportive treatment types					
Nasogastric feeding	3 (3%)	0 (0%)	3 (8%)	0 (0%)	0.13
Parenteral feeding	2 (2%)	0 (0%)	2 (5%)	0 (0%)	0.35
Transfusion of blood products	3 (3%)	1 (2%)	2 (5%)	0 (0%)	0.70
Type of surgical treatment					
Skin debridement (ward)	1 (1%)	0 (0%)	1 (3%)	0 (0%)	0.49
Skin debridement (theatre)	14 (14%)	0 (0%)	14 (36%)	0 (0%)	<0.001
Ophthalmic	2 (2%)	0 (0%)	2 (5%)	0 (0%)	0.35
None	83 (83%)	49 (98%)	23 (59%)	10 (100%)	<0.001
Complications from treatment for SCAR					
Diabetes (including steroid-induced diabetes	9 (9%)	4 (8%)	4 (10%)	1 (10%)	0.89
Osteoporosis	1 (1%)	0 (0%)	1 (3%)	0 (0%)	0.49
Opportunistic infection	7 (7%)	0 (0%)	7 (18%)	0 (0%)	0.003
Death	3 (3%)	0 (0%)	3 (7.7%)	0 (0%)	0 (0%)
None	68 (68%)	32 (64%)	26 (67%)	9 (90%)	0.30
Other[c]	8 (8%)	5 (10%)	3 (7.7%)	0 (0%)	0.47
Length of stay (at participating site, from admission to discharge) (median,IQR)	11 (6, 29) (n = 97)	11 (7, 41) (n = 47)	14 (7, 27)	4 (2, 7)	0.003
Inpatient mortality	7 (7%)	0 (0%)	7 (18%)	0 (0%)	0.003
Did the patient die as a result of SCAR?	4/7 (57%)	0 (0%)	4/7 (57%)	0 (0%)	

	Overall (n = 100)	DRESS (n = 50)	SJS/TEN (n = 39)	AGEP (n = 10)	p-value
Readmission 90 days					
No	59 (59%)	27 (54%)	25 (64%)	6 (60%)	0.43
Yes	16 (16%)	10 (20%)	4 (10%)	2 (20%)	
Unknown	25 (25%)	13 (26%)	10 (26%)	2 (20%)	
Readmission with complication of SCAR	8 (8%)	4 (8%)	4 (10%)	0 (0%)	0.040
Specialist outpatient follow up in 90 days post discharge?					
No	22 (22%)	8 (16%)	10 (26%)	3 (30%)	0.47
Yes	67 (67%)	35 (70%)	26 (67%)	6 (60%)	
Unknown	11 (11%)	7 (14%)	3 (8%)	1 (10%)	
Skin testing post discharge					
No	49 (49%)	20 (40%)	24 (62%)	4 (40%)	0.039
Yes	28 (28%)	18 (36%)	6 (15%)	4 (40%)	
Unknown	23 (23%)	12 (24%)	9 (23%)	2 (20%)	
Disability at 90 days[19]					
No	74 (74%)	36 (72%)	29 (74%)	8 (80%)	0.88
Yes	8 (8%)	4 (8%)	4 (10%)	0 (0%)	
Unknown	18 (18%)	10 (20%)	6 (15%)	2 (20%)	
Mortality 90 days					
No	75 (75%)	40 (80%)	26 (67%)	8 (80%)	0.022
Yes	11 (11%)	2 (4%)	9 (23%)	0 (0%)	
Attributable to SCAR	7/11 (64%)	1/2 (50%)	6/9 (67%)	0 (0%)	
Unknown	14 (14%)	8 (16%)	4 (10%)	2 (20%)	

Table 2. (Continued) Outcome data stratified for phenotype *Abbreviations: AGEP, acute generalized oedematous pustulosis; SJS, Stevens Johnson Syndrome; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms; IQR, interquartile range; IV, intravenous; IVIG, intravenous immunoglobulin; TPN, total parental nutrition. ᵃParaffin ointment (n = 1), antihistamines (n = 3), skin emollient Dermeze/antihistamines (n = 1), opioids (n = 1), prednisolone vaginal suppository (n = 1), cetirizine/liquid paraffin (n = 1), etanercept (n = 4), vasopressor support (n = 1), IV methylprednisolone (n = 1), oral prednisolone/betamethasone ointment/dexamethasone mouthwash/mometasone lotion (n = 1). ᵇTacrolimus (n = 1), tacrolimus/mycophenolate (n = 1). ᶜHypertension/renal impairment (n = 1), Non-ST-Elevation Myocardial Infarction (NSTEMI)/ischaemic infarcts (n = 1), unknown (n = 1), hyperpigmentation/hyperhidrosis (n = 1), facial flushing/swelling/redness (n = 1), skin dyspigmentation/hair loss (n = 1), skin bruising (n = 1), abnormal LFT/hepatitis/peripheral neuropathy (n = 1).*

phenotypic score for DRESS was 6 (probable) (IQR 5,6) and validated score for AGEP was 7 (IQR 6,8) (Table 3).

Inpatient mortality was reported in 7% (7/100) of cases, and 57% (4/7) of these cases were deemed attributable to SCAR. Regarding 90-day outcomes, 11% (11/100) of patients died and a further 8% (8/100) reported ongoing disability at 90 days (Table 2). A total of 16 patients experienced a readmission within the 90-day period (Supplementary Table 8). The all-cause mortality rate at 90 days was highest in SJS/TEN at 23.1%, compared with 4% in DRESS and 0% in AGEP. Most patients received specific immunomodulatory treatment with 77% of the cohort receiving

systemic corticosteroids and 79% receiving topical corticosteroids. A total of 16 patients were readmitted within 90 days: 20% of DRESS, 10% of SJS/TEN, and 20% of AGEP cases. Whilst a significant number reported specialist follow-up (67%), a smaller proportion reported diagnostic *in vivo* skin testing following recovery (28%).

DISCUSSION

AUS-SCAR is the first Australasian registry for SCAR, and we report the initial Australian data prior to regional expansion. We have demonstrated the establishment of a robust national co-ordinated approach to the prospective collection of SCAR phenotypic and immunophenotypic data

	Overall (n = 100)	DRESS (n = 50)	SJS/TEN (n = 39)	AGEP (n = 10)
Time in days from index rash to admission at participating site, median (IQR)	5.5 (3, 13) (n = 98)	8.5 (4, 17.5) (n = 48)	5 (3, 11)	3.5 (2, 5)
Rash components				
Erythroderma (≥90% BSA involvement	20 (20%)	12 (24%)	8 (21%)	0 (0%)
Maculopapular	68 (68%)	46 (92%)	17 (44%)	5 (50%)
Urticarial (raised oedematous non-scaly plaques)	32 (32%)	19 (38%)	8 (21%)	5 (50%)
Pustules	15 (15%)	5 (10%)	0 (0%)	10 (100%)
Vesicles, bullae or blisters	32 (32%)	6 (12%)	25 (64%)	0 (0%)
Erosion/crusting	43 (43%)	6 (12%)	37 (95%)	0 (0%)
Typical target lesions (3 zones)	3 (3%)	3 (6%)	0 (0%)	0 (0%)
Atypical targets (2 zones)	24 (24%)	5 (10%)	18 (46%)	1 (10%)
Exfoliative dermatitis/desquamation (superficial epidermal peeling)	37 (37%)	19 (38%)	13 (33%)	5 (50%)
Epidermal detachment	23 (23%)	0 (0%)	22 (56%)	0 (0%)
Distribution of Rash				
Distal extremities (arms/legs) greater than truck/torso, no mucosal surfaces affected	5 (5%)	2 (4%)	1 (3%)	2 (20%)
Distal extremities (arms/legs) greater than truck/torso, 1 mucosal surface affected (conjunctiva, lips/oral, genitalia)	3 (3%)	2 (4%)	1 (3%)	0 (0%)
Distal extremities (arms/legs) greater than trunk/torso, 2 mucosal surfaces affected	1 (1%)	0 (0%)	1 (3%)	0 (0%)
Distal extremities (arms/legs) greater than trunk/torso, 3 mucosal surfaces affected	1 (1%)	0 (0%)	1 (3%)	0 (0%)
Trunk/torso greater than extremities (arms/legs), no mucosal surfaces affected	13 (13%)	9 (18%)	0 (0%)	3 (30%)
Trunk/torso greater than extremities (arms/legs), 1 mucosal surfaces affected	7 (7%)	2 (4%)	5 (13%)	0 (0%)
Trunk/torso greater than extremities (arms/legs), 2 mucosal surfaces affected	7 (7%)	0 (0%)	7 (18%)	0 (0%)
Trunk/torso greater than extremities (arms/legs), 3 mucosal surfaces affected	4 (4%)	0 (0%)	4 (10%)	0 (0%)
Widespread (>50%), 0 mucosal surfaces affected	33 (33%)	28 (56%)	1 (3%)	4 (40%)
Widespread (>50%), 1 mucosal surface	11 (11%)	4 (8%)	6 (15%)	1 (10%)
Widespread (>50%), 2 mucosal surfaces	8 (8%)	2 (4%)	6 (15%)	0 (0%)
Widespread (>50%), 3 mucosal surfaces affected	6 (6%)	0 (0%)	6 (15%)	0 (0%)
Facial involvement				
No	15 (15%)	7 (14%)	3 (8%)	4 (40%)
Yes	83 (83%)	41 (82%)	36 (92%)	6 (60%)
Unknown	2 (2%)	2 (4%)	0 (0%)	0 (0%)
Facial oedema	49 (49%)	30 (60%)	16 (41%)	3 (30%)
Scalp involvement				
No	47 (47%)	23 (46%)	17 (44%)	6 (60%)
Yes	31 (31%)	19 (38%)	11 (28%)	1 (10%)
Unknown	22 (22%)	8 (16%)	11 (28%)	3 (30%)
Palms or sole involvement				
No	42 (42%)	22 (44%)	12 (31%)	7 (70%)
Yes	45 (45%)	21 (42%)	22 (56%)	2 (20%)
Unknown	13 (13%)	7 (14%)	5 (13%)	1 (10%)

	Overall (n = 100)	DRESS (n = 50)	SJS/TEN (n = 39)	AGEP (n = 10)
Time in days from index rash to admission at participating site, median (IQR)	5.5 (3, 13) (n = 98)	8.5 (4, 17.5) (n = 48)	5 (3, 11)	3.5 (2, 5)
Pruritus				
No	17 (17%)	3 (6%)	12 (31%)	1 (10%)
Yes	70 (70%)	44 (88%)	19 (49%)	7 (70%)
Unknown	13 (13%)	3 (6%)	8 (21%)	2 (20%)
Fever >38.5 °C on admission [within 48 h of rash onset]	50 (50%)	34 (68%)	12 (31%)	4 (40%)
Internal organ involvement (liver, renal, pulmonary) during admission	67 (67%)	43 (86%)	21 (54%)	3 (30%)
Renal Failure	21 (21%)	10 (20%)	11 (28%)	0 (0%)
Liver failure	36 (36%)	27 (54%)	8 (21%)	1 (10%)
Respiratory failure	12 (12%)	4 (8%)	8 (21%)	0 (0%)
Blood abnormality				
Platelets <150 × 10⁀9/L	24 (24%)	9 (18%)	14 (36%)	1 (10%)
WBC <4 × 10⁀9/L	15 (15%)	6 (12%)	9 (23%)	0 (0%)
Hb < 100 g/L	40 (40%)	19 (38%)	20 (51%)	1 (10%)
Atypical lymphocytes (on blood film)	15 (15%)	12 (24%)	3 (8%)	0 (0%)
Eosinophilia (>0.7 × 10⁀9/L)	45 (45%)	37 (74%)	4 (10%)	4 (40%)
Resolution <15 days	25 (25%)	11 (22%)	8 (21%)	6 (60%)
History of herpes infection (HSV 1/2) in 1 month prior to onset				
No	78 (78%)	41 (82%)	28 (72%)	8 (80%)
Yes	5 (5%)	1 (2%)	4 (10%)	0 (0%)
Unknown	17 (17%)	8 (16%)	7 (18%)	2 (20%)
History of ANY infection in 1 month prior to onset				
No	39 (39%)	22 (44%)	15 (38%)	2 (20%)
Yes	51 (51%)	27 (54%)	16 (41%)	7 (70%)
Unknown	10 (10%)	1 (2%)	8 (20%)	1 (10%)
Known concurrent viraemia (HHV6, CMV, EBV - confirmed by positive blood PCR)				
No	60 (60%)	35 (70%)	21 (54%)	3 (30%)
Yes	1 (1%)	1 (2%)	0 (0%)	0 (0%)
Unknown	39 (39%)	14 (28%)	18 (49%)	7 (70%)
History of prior skin disorder?	19 (19%)	11 (22%)	6 (15%)	1 (10%)
Phenotype specific:				N (%)
DRESS (N = 50)				
Fever >38.5 °C				40 (80%)
Enlarged lymph nodes at 2 or more sites > 1 cm				12 (24%)
Atypical lymphocytes				20 (40%)

(continued)

Phenotype specific:	N (%)
Eosinophilia ($\times$10-9/L)	
No	7 (14%)
0.7–1.49	12 (24%)
$\geq$1.5	31 (62%)
Rash	
$\geq$ 50% body	47 (94%)
Rash at least 2 of oedema, infiltration, purpura, scalling	34 (68%)
Biopsy suggestive of DRESS	39 (78%)
Pustules	6 (12%)
Blisters	6 (12%)
Number of internal organs involved	
0	4 (8%)
1	32 (64%)
2	13 (26%)
3	1 (2%)
Internal organ involved	
Renal	19 (38%)
Liver	39 (78%)
Pulmonary	1 (2%)
CNS	1 (2%)
Cardiac	3 (6%)
GI track	1 (2%)
Resolution of rash< 15 days	9 (18%)
Biological investigations - More than 3 performed to exclude alternative diagnosis	47 (94%)
RegiSCAR Score, median (IQR)	6 (5, 6) (n = 49)
SJS/TEN (N = 39)	
Total estimated BSA of rash	
< 10% BSA	6 (15%)
10–30% BSA	10 (26%)
30–50% BSA	2 (5%)
50–90% BSA	11 (28%)
90–100% BSA (erythroderma)	8 (21%)
Maximum estimated BSA of epidermal detachment (denuded/sloughed) during the course of illness	
BSA <10%	18 (46%)
BSA 10–30%	8 (21%)
BSA >30%	10 (26%)
Unknown	3 (8%)
Blistering pattern in SJS/TEN (select best match) (choice = erythema with sloughing	
Unchecked	14 (36%)
Checked	25 (64%)
Blisters on dusky macules	15 (38%)
Vesicles (<5 mm))	5 (13%)
Nikolsky's sign	21 (54%)
Blistering or bullous rash	31 (79%)

Phenotype specific:	N (%)
Did the patient present with a fever >38 °C	17 (44%)
Heart rate on admission >120 bpm	10 (26%)
Urea on admission >10 mmol/L	13 (33%)

SCORTEN score
  0-1
  2
  3
  4
  5+
	16 (41%)
	6 (15%)
	7 (18%)
	8 (21%)
	1 (3%)

Ophthalmology review	33 (85%)
Gynaecology review	12 (31%)
Urology review	8 (21%)
Has Linear IgA disease, pemphigoid, SSSS, TEN-like lupus, other autoimmune bullous disease been excluded on biopsy	35 (90%)
AGEP (N = 10)	

Type of pustules
  Follicular
  Non-follicular
  Both
  Unknown
	1 (10%)
	7 (70%)
	1 (10%)
	1 (10%)

AGEP extent of erythema/pustules
 	
  10–30% BSA
  30–50% BSA
  50–90% BSA
	2 (20%)
	4 (40%)
	4 (40%)

Distribution
  Folds predominate
  Torso
  Limbs
  Widespread
  Head and neck
  AGEP mucosal involvement
	3 (30%)
	8 (80%)
	6 (60%)
	2 (20%)
	2 (20%)
	1 (10%)

AGEP score, median (IQR)	7 (6, 8) (n = 6)

Table 3. (Continued) Clinical characteristics tables *Abbreviations: AGEP, acute generalized oedematous pustulosis; SJS, Stevens Johnson Syndrome; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms; IQR, interquartile range; BSA, Body Surface Area.*

with paired biorepository sampling. AUS-SCAR is the largest cohort published to-date from the Southern Hemisphere, including First Nations patients from our region (ie, Oceanian). AUS-SCAR lays the foundation for translational and health services research in SCAR to drive changes in prevention, diagnosis and management guidelines and policy.

With regard to phenotypic distribution, AUS-SCAR found a DRESS predominance, which is similar to a recent Thai experience,[22] but different to other Asian and European experiences[23] and may reflect the variation in clinicians involved, number of burn units currently participating (n = 3), and focus of the sites. Regarding causative drugs, beta-lactam, glycopeptide and sulfonamide antibiotics were most commonly implicated in AUS-SCAR compared to allopurinol, antiepileptics and sulfonamides in Asia and Europe.[22-27] This likely reflects the SJS/TEN predominance in these international cohorts, variance in HLA

predisposition, different prescribing patterns and, perhaps most importantly, potential ascertainment bias. Whilst the pharmacogenomic data are not presented in this manuscript, 95% of patients had DNA collected, which will further our understanding of HLA predisposition. Regarding diagnostics, more than 67% of patients had specialist care follow-up, yet only 28% proceeded to skin testing to help ascertain drug causality. Only 38% of cases had a single implicated drug, therefore there is a larger proportion where testing may have aided causality, and even in single drug implicated cases may aid safety of prescribing of class related drugs (eg, flucloxacillin DRESS and safety of cephalosporins). It further highlights the potential deficiencies in SCAR prevention and causality diagnosis.

SCAR phenotypes are associated with significant morbidity. Almost 1 in 4 required ICU admission, median length of stay (LOS) was >10 days and cases occurred in a comorbid population, including the immunocompromised. The mortality associated with SJS/TEN in our cohort closely resembled reports from the USA (14%), Thailand (17%),[22] and Korea (15.7%).[27,28] However, it was lower than other reported Asian and European experiences (mortality of 35.1% and 28%, respectively).[25,29] When comparing to a SCAR dataset from Thailand,[22] our overall inpatient mortality was numerically lower (7% vs 9.2%). Future analysis to identify predictors of mortality will be of value, however at present current cohort size is a limitation. In addition to improving mortality metrics, survival morbidity is important and remains understudied.[30] AUS-SCAR has planned routine 12-month follow up and QOL assessment;[19] the results will drive the development of minimum care standards and a benchmarking framework for clinicians and hospitals.

The current AUS-SCAR does have limitations, many of which we hope to overcome with development of the biorepository and increased site activation and patient recruitment. The current registry includes 4 burns units, with only 3 contributing data to this report. However, recruitment of all Australasian burns centres and multidisciplinary engagement is likely to improve data generalisability and include a greater representation of SJS/TEN cases. Currently, the AUS-SCAR framework remains a repository without an ability to feedback to patients post discharge. We aim to close this loop by conversion of AUS-SCAR to a clinical quality registry, and subsequent development of a minimum care standard for Australasian hospitals. We hope in the future that AUS-SCAR can inform the generation and implementation of such frameworks, provide sites with benchmarking capability and enable a patient facing element to aid access to culprit drug identification and causality testing (*in vivo* and *ex vivo/in vitro*). Further, much of the interest is improving drug causality assessment by *ex vivo* and *in vitro* work which has been piloted in SCAR,[13,20] and recent advancements in artificial intelligence and machine learning algorithm.[31] We hope that with a larger sample size international network-of-network collaborations this will also be possible. Nonetheless, the first 100 cases of AUS-SCAR provide the establishment of the registry as a biorepository as well as an insight into SCAR in a varied Southern Hemisphere population that provides a roadmap to focus the research agenda and care provided to SCAR patients.

Abbreviations

AGEP, acute generalized oedematous pustulosis; **ATSI**, Aboriginal and Torres Strait Islanders; **BSA**, Body Surface Area; **CCI**, age-adjusted Charlson Comorbidity Index; **DRESS**, drug reaction with eosinophilia and systemic symptoms; **GBFDE**, Generalized bullous fixed drug eruption; **HLA**, Human Leukocyte Antigen; **IV**, intravenous; **IVIG**, intravenous immunoglobulin; **IQR**, interquartile range; **NSAID**, non-steroidal anti-inflammatory drug; **PPI**, proton-pump inhibitors; **SCAR**, Severe Cutaneous Adverse Reactions; **SJS**, Stevens Johnson Syndrome; **SSRI**, selective serotine receptor inhibitors; **TEN**, toxic epidermal necrolysis; **TPN**, total parental nutrition.

Availability of data

Data supporting this study is not available publicly.

Author contributions

Conception and design of the study: Trubiano, Phillips, James, Vogrin.
Acquisition, analysis, or interpretation of data: all authors.
Statistical analysis: Vogrin.

Drafting the article or critical revision of the manuscript for important intellectual consent: all authors.
All authors approved the publication of the manuscript.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.100936.

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