Supplementary Table 1 – Participating site characteristics

Site	State	Burns Unit	Total Hospital Bed numbers
Austin Health	VIC	N	800
Alfred Health	VIC	Y	638
Royal Melbourne Hospital	VIC	N	571
St Vincent's Hospital Melbourne	VIC	N	793
Peter MacCallum Cancer Centre	VIC	N	312
Eastern Health (Box Hill Hospital)	VIC	N	621
Monash Health	VIC	N	640
St Vincent's Hospital Sydney	NSW	N	402
Nepean Hospital	NSW	N	520
Campbelltown Hospital	NSW	N	306
Royal North Shore Hospital	NSW	Y	600
Royal Adelaide Hospital	SA	Y	800
Royal Darwin Hospital	NT	N	360
Royal Brisbane and Women's Hospital	QLD	Y	983

Abbreviations: VIC, Victoria; NSW, New South Wales; SA, South Australia; NT, Northern Territory; QLD, Queensland.

Supplementary Table 2 – Biospecimen repository collection

		Overall (N=100)	DRESS (N=50)	SJS/TEN (N=39)	AGEP (N=10)	p-value
Acute samples collected		45 (45.0%)	21 (42%)	18 (46%)	6 (60%)	0.34
DNA collected		95 (95.0%)	49 (98%)	35 (90%)	10 (100%)	0.22
DNA sample type						
	Blood	27 (27.0%)	14 (28%)	11 (28%)	1 (10%)	
	Saliva	35 (35.0%)	21 (42%)	9 (23%)	5 (50%)	
	PBMC	33 (33.0%)	14 (28%)	15 (38%)	4 (40%)	
HLA typing performed		92 (92.0%)	48 (96%)	34 (87%)	9 (90%)	0.48
Blood collected for PBMC extraction		57 (57.0%)	26 (52%)	24 (62%)	6 (60%)	0.58
Skin collection		24 (24.0%)	7 (14%)	16 (41%)	1 (10%)	0.007
Blister fluid collection		8 (8.0%)	0 (0%)	7 (18%)	0 (0%)	0.003

Abbreviations: HLA, Human Leukocyte Antigen; PBMC, Peripheral Blood Mononuclear Cells

Supplementary Table 3 – Causality assessment undertaken for each case by site investigators

		Overall (N=100)	DRESS (N=50)	SJS/TEN (N=39)	AGEP (N=10)
Was the SCAR suspected to be caused by a drug?					
	No	2 (2%)	1 (2%)	1 (3%)	0 (0%)
	Yes	96 (96%)	49 (98%)	37 (95%)	9 (90%)
	Missing	2 (2%)	0 (0%)	1 (3%)	1 (10%)
Was the drug being administered at time of rash onset?					
	No	12 (12%)	6 (12%)	5 (13%)	1 (10%)
	Yes	85 (85%)	44 (88%)	32 (82%)	8 (80%)
	Missing	3 (3%)	0 (0%)	2 (5%)	1 (10%)
Was the drug being continuously administered for more than 8 weeks prior to rash?					
	No	96 (96%)	49 (98%)	37 (95%)	9 (90%)

		Overall (N=100)	DRESS (N=50)	SJS/TEN (N=39)	AGEP (N=10)
	Yes	1 (1%)	1 (2%)	0 (0%)	0 (0%)
	Missing	3 (3%)	0 (0%)	2 (5%)	1 (10%)
Was the drug likely to be present in serum at time of rash onset [within 5 half lives]?]					
	No	1 (1%)	1 (2%)	0 (0%)	0 (0%)
	Yes	10 (10%)	4 (8%)	5 (13%)	1 (10%)
	Missing	89 (89%)	45 (90%)	34 (87%)	9 (90%)
What drug class?					
	Antibiotic	60 (60%)	31 (62%)	20 (51%)	9 (90%)
	Non-antibiotic	37 (37%)	19 (38%)	17 (44%)	0 (0%)
	Missing	3 (3%)	0 (0%)	2 (5%)	1 (10%)
Was there only a single implicated causal drug?					
	No	59 (59%)	28 (56%)	23 (59%)	8 (80%)

		Overall (N=100)	DRESS (N=50)	SJS/TEN (N=39)	AGEP (N=10)
	Yes	38 (38%)	22 (44%)	14 (36%)	1 (10%)
	Missing	3 (3%)	0 (0%)	2 (5%)	1 (10%)
Number of implicated drugs, median (IQR)		3 (2, 4) (n=60)	2 (2, 3) (n=29)	3 (2, 4) (n=23)	2 (2, 3) (n=8)
Was one or more antibiotics implicated in drug causality?					
	No	30 (30%)	16 (32%)	13 (33%)	0 (0%)
	Yes	67 (67%)	34 (68%)	24 (62%)	9 (90%)
	Missing	3 (3%)	0 (0%)	2 (5%)	1 (10%)
Temporal association with vaccination?					
	No	96 (96%)	47 (94%)	38 (97%)	10 (100%)
	Yes	3 (3%)	3 (6%)	0 (0%)	0 (0%)
	Missing	1 (1%)	0 (0%)	1 (3%)	0 (0%)
Temporal association with IV contrast?					

		Overall (N=100)	DRESS (N=50)	SJS/TEN (N=39)	AGEP (N=10)
	No	93 (93%)	46 (92%)	36 (92%)	10 (100%)
	Yes	5 (5%)	3 (6%)	2 (5%)	0 (0%)
	Missing	2 (2%)	1 (2%)	1 (3%)	0 (0%)
Autoantibodies present?					
	No	54 (54%)	26 (52%)	24 (62%)	4 (40%)
	Yes	19 (19%)	11 (22%)	7 (18%)	0 (0%)
	Unknown	27 (27%)	13 (26%)	8 (21%)	6 (60%)
Autoantibody types					
	ANA	43 (43%)	19 (38%)	20 (51%)	3 (30%)
	ENA	27 (27%)	7 (14%)	17 (44%)	3 (30%)
	dsDNA	25 (25%)	6 (12%)	16 (41%)	3 (30%)
	Other	13 (13%)	4 (8%)	9 (23%)	0 (0%)

Abbreviations: ANA, Antinuclear antibody; ENA, Extractable Nuclear Antigen Antibodies; dsDNA, double stranded DNA; IQR, interquartile range; IV, intravenous

Supplementary Table 4: All implicated drugs, stratified for each phenotype.

		Overall (n=256)	DRESS (n=135)	SJS/TEN (n=99)	AGEP (n=21)
Drug classification					
	Allopurinol	13 (5.0%)	7 (5.1%)	6 (6.0%)	0 (0.0%)
	Aminoglycoside	1 (0.4%)	1 (0.7%)	0 (0.0%)	0 (0.0%)
	Anaesthetic	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (4.8%)
	Anti-diabetic	2 (0.8%)	0 (0.0%)	2 (2.0%)	0 (0.0%)
	Anticoagulant	4 (1.6%)	3 (2.2%)	1 (1.0%)	0 (0.0%)
	Antiemetic	2 (0.8%)	2 (1.5%)	0 (0.0%)	0 (0.0%)
	Antiepileptic	16 (6.2%)	7 (5.1%)	9 (9.0%)	0 (0.0%)
	Antifungal	13 (5.0%)	9 (6.6%)	2 (2.0%)	2 (9.5%)
	Antituberculosis	2 (0.8%)	2 (1.5%)	0 (0.0%)	0 (0.0%)
	Antivirals	1 (0.4%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
	Carbapenem	10 (3.9%)	5 (3.7%)	5 (5.0%)	0 (0.0%)
	Cephalosporin	27 (10.5%)	14 (10.3%)	9 (9.0%)	4 (19.0%)
	Check point inhibitor	1 (0.4%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
	Chemotherapeutic	9 (3.5%)	4 (2.9%)	5 (5.0%)	0 (0.0%)
	Contrast	3 (1.2%)	3 (2.2%)	0 (0.0%)	0 (0.0%)
	Diuretic	3 (1.2%)	1 (0.7%)	2 (2.0%)	0 (0.0%)
	Flozin	1 (0.4%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
	Fluoroquinolone	6 (2.3%)	6 (4.4%)	0 (0.0%)	0 (0.0%)
	Glycopeptide	20 (7.8%)	13 (9.6%)	6 (6.0%)	1 (4.8%)

		Overall (n=256)	DRESS (n=135)	SJS/TEN (n=99)	AGEP (n=21)
	Iron	1 (0.4%)	1 (0.7%)	0 (0.0%)	0 (0.0%)
	Lincosamide	4 (1.6%)	2 (1.5%)	1 (1.0%)	1 (4.8%)
	Monobactam	1 (0.4%)	1 (0.7%)	0 (0.0%)	0 (0.0%)
	NSAID/Analegesics	10 (3.9%)	2 (1.5%)	6 (6.0%)	1 (4.8%)
	Nitroimidazole	3 (1.2%)	1 (0.7%)	2 (2.0%)	0 (0.0%)
	Other - antibiotic	7 (2.7%)	4 (2.9%)	2 (2.0%)	1 (4.8%)
	Other - nonantibiotic	15 (5.8%)	11 (8.1%)	4 (4.0%)	0 (0.0%)
	PPI	10 (3.9%)	1 (0.7%)	9 (9.0%)	0 (0.0%)
	Penicillin	37 (14.3%)	19 (14.0%)	9 (9.0%)	9 (42.9%)
	Pholcodine	1 (0.4%)	1 (0.7%)	0 (0.0%)	0 (0.0%)
	SSRI	2 (0.8%)	0 (0.0%)	2 (2.0%)	0 (0.0%)
	Sulfonamide	20 (7.8%)	9 (6.6%)	11 (11.0%)	0 (0.0%)
	Tetracycline	3 (1.2%)	1 (0.7%)	1 (1.0%)	1 (4.8%)
	Thyroxine	1 (0.4%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
	Uricosuric Agents	2 (0.8%)	0 (0.0%)	2 (2.0%)	0 (0.0%)
	Vaccine	6 (2.3%)	6 (4.4%)	0 (0.0%)	0 (0.0%)
Drug Class					
	Antibiotic	150 (58.1%)	85 (62.5%)	47 (47.0%)	18 (85.7%)
	Non-antibiotic	108 (41.9%)	51 (37.5%)	53 (53.0%)	3 (14.3%)

		Overall (n=256)	DRESS (n=135)	SJS/TEN (n=99)	AGEP (n=21)
Was this the most likely implicated drug?					
	No	139 (53.9%)	69 (50.7%)	60 (60.0%)	10 (47.6%)
	Yes	117 (45.3%)	67 (49.3%)	40 (40.0%)	9 (42.9%)
	Missing	2 (0.8%)	0 (0.0%)	0 (0.0%)	2 (9.5%)
Total drug duration (day), median (IQR)		8 (3, 28) (n=235)	8 (3, 28) (n=123)	15 (4, 29) (n=91)	3 (.5, 8) (n=20)
Drug latency (day)*, median (IQR)		15 (5, 24) (n=241)	15 (5, 25) (n=127)	21 (7, 27) (n=93)	2.5 (1, 8) (n=20)
Was the drug commenced pre onset of rash?					
	No	19 (7.4%)	16 (11.8%)	2 (2.0%)	1 (4.8%)
	Yes	236 (91.5%)	118 (86.8%)	97 (97.0%)	20 (95.2%)
	Missing	3 (1.2%)	2 (1.5%)	1 (1.0%)	0 (0.0%)
On day of rash onset > 5 half-lives of the drug elapsed since it was last taken					
	No	193 (74.8%)	104 (76.5%)	72 (72.0%)	16 (76.2%)
	Yes	56 (21.7%)	28 (20.6%)	26 (26.0%)	2 (9.5%)

		Overall (n=256)	DRESS (n=135)	SJS/TEN (n=99)	AGEP (n=21)
	Missing	9 (3.5%)	4 (2.9%)	2 (2.0%)	3 (14.3%)
ALDEN Score, median (IQR)				4 (1, 5) (n=97)	
Naranjo Score, median (IQR)		4 (3, 5) (n=220)	4 (4, 5) (n=106)	4 (3, 4.5) (n=96)	4 (4, 5) (n=17)
History of same reaction to same drug?					
	No	243 (94.2%)	128 (94.1%)	96 (96.0%)	19 (90.5%)
	Yes	11 (4.3%)	7 (5.1%)	3 (3.0%)	0 (0.0%)
	Missing	4 (1.6%)	1 (0.7%)	1 (1.0%)	2 (9.5%)
History of same reaction to similar drug (same class)?					
	No	244 (94.6%)	129 (94.9%)	98 (98.0%)	16 (76.2%)
	Yes	8 (3.1%)	5 (3.7%)	0 (0.0%)	3 (14.3%)
	Missing	6 (2.3%)	2 (1.5%)	2 (2.0%)	2 (9.5%)
History of different reaction to same drug?					
	No	252 (97.7%)	135 (99.3%)	97 (97.0%)	19 (90.5%)
	Yes	1 (0.4%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
	Missing	5 (1.9%)	1 (0.7%)	2 (2.0%)	2 (9.5%)

		Overall (n=256)	DRESS (n=135)	SJS/TEN (n=99)	AGEP (n=21)
History of different reaction to similar drug (same class)?					
	No	246 (95.3%)	132 (97.1%)	95 (95.0%)	18 (85.7%)
	Yes	4 (1.6%)	1 (0.7%)	2 (2.0%)	1 (4.8%)
	Missing	8 (3.1%)	3 (2.2%)	3 (3.0%)	2 (9.5%)

Abbreviations: PPI, proton pump inhibitor; NSAID, non-steroid anti-inflammatory; SSRI, selective serotonin receptor inhibitor; IQR, interquartile range

Note: (n = drug not n = participant):

*Duration of drug given prior to rash onset

Supplementary Table 5: Summary of Patient Comorbidities Charlson Comorbidity Index and Patient Comorbidities Immunocompromised Status

	Total (n=100)	DRESS (n=50)	SJS/TEN (n=39)	AGEP (n=10)	p-value
Patient Comorbidities Charlson Comorbidity Index					
Myocardial infarct	2 (2.0%)	1 (2%)	1 (3%)	0 (0%)	0.88
Congestive heart failure	8 (8.0%)	3 (6%)	4 (10%)	1 (10%)	0.74
Peripheral vascular disease	1 (1.0%)	1 (2%)	0 (0%)	0 (0%)	0.61
Cerebrovascular disease (except hemiplegia)	2 (2.0%)	2 (4%)	0 (0%)	0 (0%)	0.37
Dementia	2 (2.0%)	0 (0%)	2 (5%)	0 (0%)	0.21
Chronic pulmonary disease	6 (6.0%)	1 (2%)	3 (8%)	2 (20%)	0.080
Connective tissue disease	8 (8.0%)	4 (8%)	4 (10%)	0 (0%)	0.57
Ulcer disease	4 (4.0%)	0 (0%)	4 (10%)	0 (0%)	0.040
Mild liver disease	9 (9.0%)	3 (6%)	6 (15%)	0 (0%)	0.18
Diabetes (without complications)	9 (9.0%)	5 (10%)	2 (5%)	2 (20%)	0.33
Diabetes with end organ damage	6 (6.0%)	2 (4%)	3 (8%)	1 (10%)	0.66
Hemiplegia or paraplegia	1 (1.0%)	1 (2%)	0 (0%)	0 (0%)	0.61
Mod or severe renal disease	8 (8.0%)	4 (8%)	3 (8%)	1 (10%)	0.97
Solid tumor (non-metastatic)	5 (5.0%)	3 (6%)	2 (5%)	0 (0%)	0.73
Leukemia	4 (4.0%)	3 (6%)	1 (3%)	0 (0%)	0.57
Lymphoma, Multiple myeloma	5 (5.0%)	5 (10%)	0 (0%)	0 (0%)	0.076
Mod or severe liver disease [cirrhosis + PHTN or transplant)	4 (4.0%)	1 (2%)	3 (8%)	0 (0%)	0.32
Metastatic solid tumor	7 (7.0%)	1 (2%)	6 (15%)	0 (0%)	0.033

AIDS	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Patient Comorbidities Immunocompromised Status					
Immunocompromised - any	38 (38.0%)	18 (36%)	17 (44%)	3 (30%)	0.65
Autoimmune/connective tissue	7 (7.0%)	2 (4%)	5 (13%)	0 (0%)	0.18
Haematological malignancy (last 5 years)	10 (10.0%)	9 (18%)	1 (3%)	0 (0%)	0.030
Stem cell transplant	3 (3.0%)	2 (4%)	1 (3%)	0 (0%)	0.78
Solid organ transplant	1 (1.0%)	1 (2%)	0 (0%)	0 (0%)	0.61
Solid tumour malignancy (last 5 years)	7 (7.0%)	0 (0%)	7 (18%)	0 (0%)	0.003
HIV (CD4< 500)	1 (1.0%)	0 (0%)	0 (0%)	1 (10%)	0.011
HIV (CD4>500)	0(0%)	0(0%)	0(0%)	0(0%)	
Prednisolone > 10mg daily for 1 month	4 (4.0%)	1 (2%)	3 (8%)	0 (0%)	0.32
End stage kidney disease on dialysis	3 (3.0%)	1 (2%)	1 (3%)	1 (10%)	0.39
End stage chronic liver disease	2 (2.0%)	0 (0%)	2 (5%)	0 (0%)	0.21
Splenectomy	2 (2.0%)	0 (0%)	1 (3%)	1 (10%)	0.12
Primary immunodeficiency	0(0%)	0(0%)	0(0%)	0(0%)	
Other immunosuppressive medications	9 (9.0%)	3 (6%)	6 (15%)	0 (0%)	0.18

Supplementary Table 6: History of previous skin disorder

Factor	Level	Total (n=100)	AGEP (n=10)	DRESS (n=50)	SJS/TEN (n=39)	p-value
History of prior skin disorder?	No	80 (81%)	9 (90%)	39 (78%)	32 (84%)	0.69
	Yes	19 (19%)	1 (10%)	11 (22%)	6 (16%)	
Type	Eczema	7 (7.0%)	1 (10%)	5 (10%)	1 (3%)	0.34
	Psoriasis	3 (3.0%)	0 (0%)	2 (4%)	1 (3%)	1.00
	Bullous pemphigoid	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	Cutaneous cell lymphoma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	Cutaneous lupus	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	Other	11 (11.0%)	0 (0%)	6 (12%)	4 (10%)	
Other skin disorder, specify						
	Acne			1 (17%)	1 (25%)	
	Chronic lower limb lymphoedema			1 (17%)	0 (0%)	
	Diabetic foot ulcers			1 (17%)	0 (0%)	
	Lichen planus (oral, and patchy on skin)			1 (17%)	0 (0%)	
	SLE / undifferentiated connective tissue disease but no prior cutaneous lupus rash			0 (0%)	1 (25%)	
	crusted scabies			1 (17%)	0 (0%)	
	melanoma			0 (0%)	1 (25%)	
	pustular psoriasis			1 (17%)	0 (0%)	

	unclear ? eczema; connective tissue disease lupus/ rheumatoid?	0 (0%)	1 (25%)	

Supplementary Table 7: ICU admission details according to Patient Comorbidities Charlson Comorbidity Index and Patient Comorbidities Immunocompromised Status

	No ICU (n=72)	ICU (n=28)	p-value
Patient Comorbidities Charlson Comorbidity Index			
CCI index	2 (0, 4)	3 (1.5, 6)	0.029
Myocardial infarct	1 (1%)	1 (4%)	0.48
Congestive heart failure	5 (7%)	3 (11%)	0.53
Peripheral vascular disease	1 (1%)	0 (0%)	0.53
Cerebrovascular disease (except hemiplegia)	1 (1%)	1 (4%)	0.48
Dementia	2 (3%)	0 (0%)	0.37
Chronic pulmonary disease	4 (6%)	2 (7%)	0.76
Connective tissue disease	8 (11%)	0 (0%)	0.066
Ulcer disease	1 (1%)	3 (11%)	0.033
Mild liver disease	5 (7%)	4 (14%)	0.25
Diabetes (without complications)	6 (8%)	3 (11%)	0.71
Diabetes with end organ damage	5 (7%)	1 (4%)	0.52
Hemiplegia or paraplegia	1 (1%)	0 (0%)	0.53
Mod or severe renal disease	3 (4%)	5 (18%)	0.023
Solid tumor (non metastatic)	5 (7%)	0 (0%)	0.15
Leukemia	1 (1%)	3 (11%)	0.033
Lymphoma, Multiple myeloma	3 (4%)	2 (7%)	0.54
Mod or severe liver disease [cirrhosis + PHTN or transplant)	0 (0%)	4 (14%)	0.001
Metastatic solid tumor	4 (6%)	3 (11%)	0.36

AIDS	0 (0%)	0 (0%)	
Patient Comorbidities Immunocompromised Status			
Immunocompromised	25 (35%)	13 (46%)	0.28
Autoimmune/connective tissue	7 (10%)	0 (0%)	0.087
Haematological malignancy (last 5 years)	5 (7%)	5 (18%)	0.10
Stem cell transplant	1 (1%)	2 (7%)	0.13
Solid organ transplant	1 (1%)	0 (0%)	0.53
Solid tumour malignancy (last 5 years)	4 (6%)	3 (11%)	0.36
HIV (CD4< 500)	1 (1%)	0 (0%)	0.53
HIV (CD4>500)	0 (0%)	0 (0%)	
Prednisolone > 10mg daily for 1 month	2 (3%)	2 (7%)	0.32
End stage kidney disease on dialysis	2 (3%)	1 (4%)	0.83
End stage chronic liver disease	0 (0%)	2 (7%)	0.022
Splenectomy	1 (1%)	1 (4%)	0.48
Primary immunodeficiency	0 (0%)	0 (0%)	
Other immunosuppressive medications	5 (7%)	4 (14%)	0.25

Supplementary Table 8: Free text reports from investigators for reasons for readmission in the 16 patients reported in the analysis.

Reasons for readmission
finger nail loss and infection, ciprofloxacin immediate reaction (rash, 38C, abdo & chest pain, angioedema, tachycardia, hypotension, collapse ? anaphylaxis)
Recurrent rash 24-06-2020
Worsening abdominal pain
Bilateral hip and back pain in context of MSSA bacteraemia
increasing prutitis and confusion from prednisolone
Elevated LFTs, rash, jaundice
Fever and rash
Diabetes mellitus due to non-steroid drug
Flare 80% BSA rash, fever when Pred reduced to 37.5;DDx also started Dapsone 4.5weeks prior
Progressive lymphoma
ongoing severe worsening rash, subjective fevers
? drug overdose
Sepsis
hyperkalaemia, painful tongue, fluid overload
took his own leave during first admission, ran out of medication, re-presented with recrudescence of skin reaction with oedema
for lung surgery Aug 2020
Increasing pain and inability to cope at home due to MSSA bactaraemia
Elevated LFTs, body aches
Progressive lymphoma
MSSA bacteraemia
Progressive lymphoma
Progressive lymphoma

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2. Sidoroff A, Halevy S, Bavinck JN, Vaillant L, Roujeau JC. Acute generalized exanthematous pustulosis (AGEP)--a clinical reaction pattern. Journal of cutaneous pathology. 2001;28(3):113-9.