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The Safety of Antibiotic Skin Testing in Severe T-cell-Mediated Hypersensitivity of immunocompetent and immunocompromised hosts.

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To the Editor,

Severe T-cell mediated hypersensitivities commonly have antibiotics implicated in causality, and associated with significant morbidity and mortality (21–25%)¹. Although all severe cutaneous adverse drug reactions (SCAR), are severe T-cell-mediated, including drug reaction with eosinophilia and system symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalized exanthematous pustulosis (AGEP), their immune mediators, specific mechanisms and clinical presentation vary². Antibiotics are amongst the most commonly implicated drugs in severe T-cell-mediated and at the onset of it is not uncommon for multiple drugs including antibiotics to be implicated. In immunocompromised hosts (ICHs), in particular, ascertaining drug causality is vital to enabling safe future therapies¹. The sensitivity of current *in vivo* testing modalities varies,

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performing better for certain phenotypes over others (SJS; 20–30% vs. DRESS; 60–70%), with limited data in ICH. *In vivo* testing, primarily patch testing (PT) has been performed safely in severe T-cell-mediated hypersensitivity³, yet many international guidelines suggest it is a contraindication or relative contraindication to intradermal testing^{4–6}. In particular, there is often concern regarding employing such *in vivo* testing within six months of the reaction, or in vulnerable hosts, such as ICH. Our objective was to evaluate the safety of *in vivo* skin testing in antibiotic-associated severe T-cell-mediated hypersensitivities in both the immunocompetent and ICH.

We reviewed patients with a history of severe antibiotic-associated T-cell mediated hypersensitivity (SCAR and generalized fixed drug eruption[FDE]) who had undergone intradermal [IDT] or patch testing [PT] between May 2015 and June 2018 at Austin Health and Peter MacCallum Cancer Centre in Melbourne, Australia. Patients were identified from a prospectively collected dataset from a prior cohort study (Ethics Approval Number: 15/Austin/75). Patients were divided into the study cohort (ICH) versus control cohort (immunocompetent, non-ICH). An ICH was defined as a transplant recipient, recipient of prednisolone more than 10mg/day for 1 month, autoimmune/connective tissue disorder, HIV (CD4+/CD8+ T-cells < 500 cells/ μ L) or haematological/solid cancer malignancy (chemotherapy within last 12 months). All cases had at least one antibiotic administered within 5 half-lives of onset of rash, a Naranjo score of > 4, phenotype confirmed by dermatologist and had at least three investigations to exclude common alternative causes (e.g. HSV 1 or 2, *Mycoplasma pneumoniae*, ANA). *In vivo* testing (IDT and/or PT) was performed as per previously published protocols⁷, utilizing the highest non-irritating concentrations where possible^{6, 8} [Supplementary Table 1]. Skin testing was performed at least 6 weeks following the resolution of cutaneous manifestations in patients who had a phenotype consistent with a delayed reaction (> 6 hour from dosing). Antibiotic IDT was performed using a sterile, diluted commercially available intravenous preparation of the antibiotic injected at 0.02 ml intradermally in the forearm or the specific site of previous reactivity in the cases of FDE. A positive IDT was considered to be a >5mm erythematous, raised and indurated or infiltrative lesion present at 6–48 hours post IDT (at the site of IDT).⁹ Patch tests were applied with the antibiotic compounded in petrolatum to a flat portion of the back and fixed for 48 hours prior to removal. A positive patch test was graded according to previously published International Contact Dermatitis Research Group Definitions¹⁰. Patients were followed for 90 days post testing for adverse event.

There were 488 patients who completed allergy testing during the study period, 45% (221/488) with a history of delayed antibiotic-associated cutaneous reaction. Of the 221, 34 patients had a history consistent with an antibiotic-associated SCAR or generalized FDE. Of these, 31/33 (94%) underwent IDT and/or PT to multiple implicated drugs of which there were 50 implicated antibiotics – betalactam 23 (46), glycopeptide 11 (22%), sulfonamide antibiotic 6 (11%), macrolide 6 (0%), metronidazole 2 (4%), fluoroquinolone 1 (2%) and linezolid 1 (2%). The median drug latency was 7 days (IQR 3, 21) – DRESS (11 days; IQR 3,23), SJS/TEN (4 days; IQR 3,26) and generalized FDE (1 day; IQR 1,1). Of those who underwent testing, 17/33 (52%) were ICH. The demographics and clinical characteristics of both cohorts are outlined in Table I. Twenty-eight (90%) underwent IDT, 14 (45%) PT and 10 (32%) combination of both (Table I), with 13 (42%) positive skin test results, 38% (6/16)

for ICH versus 47% non-ICH (7/15), $p = 0.71$. The median time (days) from severe T-cell-mediated hypersensitivity to follow-up patch and/or IDT was 253 days (IQR 91,401), including 316 (IQR 194,458) for SJS/TEN, 169 (IQR 86,3336) for DRESS and 307 (IQR 194,458) for generalized FDE. The range (days) from DRESS onset to intradermal testing was 44–2614 days. There were no cases of systemic adverse event noted in either cohort at time of testing (day 0) or during follow-up (90 days post). Two ICH patients (6.5%) died post 30 day follow up, related to progression of their haematological or solid malignancy.

This prospective multicentre cohort data from two centers in Melbourne (Australia) support the safety of *in vivo* testing for severe T-cell-mediated hypersensitivity, including SCAR³. This data is however limited by the small study numbers and low rates of skin test positivity, especially in the ICH. Nonetheless, there were no systemic or reported sequelae from IDT even when performed within 6 months of the original reaction. IDT whilst performed sporadically for decades in the literature^{11, 12}, is frequently avoided outside of Europe due to lack of availability of sterile, pharmacy prepared and FDA approved reagents for IDT and concerns of systemic adverse reactions, especially amongst ICH and vulnerable hosts. Although absent from our study, there are reports of systemic adverse events with testing in the literature^{13, 14}, therefore vigilance and specialist oversight is always required, however the morbidity and potential opportunities for medication errors post severe T-cell-mediated hypersensitivity without a clear label is also evident.

Whilst there is increasing evidence to support the safety of skin testing in T-cell mediated reactions, any testing modality in isolation still has a significantly less than 100% negative predictive value, the utility of *in vivo* testing especially when combined with clinical causality assessment and *ex vivo* diagnostics appears to significantly increase the sensitivity of testing for delayed T-cell mediated reactions¹⁵. This data despite its limitations supports the safety of skin testing, especially in our most vulnerable patients such as ICH. It should prompt new guidelines to support the use of skin testing, in particular IDT for DRESS or non-specific exanthems in carefully selected patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical implications box

Trubiano and colleagues demonstrate the safety of skin testing in immunocompetent and immunocompromised hosts with antibiotic-associated severe T-cell-mediated hypersensitivity. This complements and furthers international data, helping shape future guidelines regarding the safety of skin testing in severe T-cell-mediated hypersensitivity, especially in immunocompromised hosts.

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Table I.

Clinical and testing characteristics of cohort

Patient characteristic	Patient group		Overall (n = 31)	P value
	ICH (n = 16)	Non-ICH (n = 15)		
Age (y), median (IQR)	66 (58–75)	44 (25–69)	59 (44–70)	0.008
Sex: male, n (%)	10 (63)	9 (60)	19 (61)	0.886
Age-adjusted CCI, median (IQR)	5 (5–8)	4 (2–5)	5 (3–6)	0.02
Phenotype				0.533
SJS/TEN	1 (6)	3 (20)	4(13)	
DRESS	12 (75)	10 (67)	22 (71)	
AGEP	1 (6)	0	1 (3)	
FDE	2(13)	2(13)	4(13)	
Ethnicity				0.94
White	14 (88)	13 (87)	27 (87)	
Asian	2(13)	2(13)	4(13)	
Naranjo score, median (IQR)	4 (3–4)	3 (3–4)	4 (3–4)	0.392
RegiSCAR, median (IQR) (n = 22)	4 (4–5.5)	4 (3–5)	4 (4–5)	0.798
ALDEN score, median (IQR)	3 (3–3)	3 (2–3)	3 (3–3)	0.674
Hospitalization	13 (81)	14 (93)	28 (85)	0.135
Implicated antibiotics (n)	25	25	50	—
Latency (d), median (IQR) *	10 (3–22)	7 (3–21)	7 (3–21)	0.855
>1 antibiotic implicated, n (%)	7(41)	6 (40)	13 (43)	1
PT or IDT (n = 31), n (%)				
Positive	6 (38)	7 (47)	13 (42)	0.722
PT (n = 13), n (%)				
Performed	7 (43)	6 (40)	13 (42)	0.833
Positive	1 (14)	2 (33)	3 (21)	0.56
IDT (n = 28), n (%)				
Performed	13 (81)	15 (100)	28 (90)	0.078
Positive	5 (39)	6 (40)	11 (36)	1
PT & IDT (n = 10), n (%)				
Positive †	0	2(13)	2(7)	0.226
IDT positive (n = 11) to >1 antibiotic, n (%)	3 (19)	4(26)	7 (22)	0.685
> 1 penicillin	3 (100)	2 (50)	5 (71)	
Penicillin and cephalosporin	0	1 (25)	1 (14)	
Positive for antibiotic class tested, n (%)				
Penicillin	4(25)	4 (27)	8 (26)	0.345
Cephalosporin	0	2(13)	2(7)	
Carbapenem	0	1 (7)	1 (3)	
Trimethoprim	1 (6)	0	1 (3)	
Metronidazole	1 (6)	0	1 (3)	

CCI, Charlson comorbidity index.

* Latency–Period from complete resolution of cutaneous findings of T–cellemediated hypersensitivity until skin testing.

[†] Same drugs positive on both ceftriaxone and amoxicillin.

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