

The safety of antibiotic skin testing in severe T-cell-mediated hypersensitivity of immunocompetent and immunocompromised hosts

Jason A. Trubiano, MBBS, PhD^{a,b,c,d},

Abby P. Douglas, MBBS^{b,d}, Michelle Goh, MBBS^{e,f},

Monica A. Slavin, MBBS, PhD^{b,d}, and

Elizabeth J. Phillips, MD^{g,h}



Clinical Implications

- Trubiano et al 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.

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 (SCARs) 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 vary.² Antibiotics are among the most commonly implicated drugs in severe T-cell-mediated hypersensitivities 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 therapies.¹ The sensitivity of current *in vivo* testing modalities varies, 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 hypersensitivity,³ yet many international guidelines do not comment on suitability or suggest that it is a contraindication or relative contraindication to intradermal testing.⁴⁻⁶ In particular, there is often concern regarding using such *in vivo* testing within 6 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 testing [IDT] or 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 data set from a previous cohort study (Ethics Approval Number: HREC/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 10 mg/d for 1 month, suffering from autoimmune/connective tissue disorder, HIV (CD4+/CD8+ T cells < 500 cells/ μ L), or hematological/solid cancer malignancy (chemotherapy within last 12 months). All cases had at least 1 antibiotic administered within 5 half-lives of onset of rash, a Naranjo score of more than 4, phenotype confirmed by dermatologist, and had at least 3 investigations to exclude common alternative causes (eg, herpes simplex virus [HSV] 1 or 2, *Mycoplasma pneumoniae*, and antinuclear antigen [ANA]). *In vivo* testing (IDT and/or PT) was performed as per previously published protocols,⁷ using the highest nonirritating concentrations where possible^{6,8} (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). 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 hours 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 result was considered to be a greater than 5 mm erythematous, raised, and indurated or infiltrative lesion present at 6 to 48 hours after 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 before removal. A positive patch test result was graded according to previously published International Contact Dermatitis Research Group Definitions.¹⁰ 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 of 488) with a history of delayed antibiotic-associated cutaneous reaction. Of the 221, 33 patients had a history consistent with an antibiotic-associated SCAR or generalized FDE. Of these, 31 of 33 (94%) underwent IDT and/or PT to multiple implicated drugs of which there were 50 implicated antibiotics—beta-lactam 23 (46%), glycopeptide 11 (22%), sulfonamide antibiotic 6 (11%), macrolide 6 (12%), metronidazole 2 (4%), fluoroquinolone 1 (2%), and linezolid 1 (2%). The median drug latency was 7 days (interquartile range [IQR], 3-21 days)—DRESS (11 days; IQR, 3-23 days), SJS/TEN (4 days; IQR, 3-26 days), and generalized FDE (1 day; IQR, 1-1 day). Of those who underwent testing, 16 of 31 (52%) were ICH. The demographic 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 of 16) for ICH versus 47% for non-ICH (7 of 15), $P = .71$. The median time (days) from severe T-cell-mediated hypersensitivity to follow-up patch and/or IDT was 253 days (IQR, 91-401 days), including 316 (IQR, 194-458 days) for SJS/TEN, 169 (IQR, 86-336 days) for DRESS, and 307 (IQR, 194-458 days) for generalized FDE. The range (days) from DRESS onset to intradermal testing was 44 to 2614 days. There were no cases

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-cell-mediated hypersensitivity until skin testing.

†Same drugs positive on both ceftriaxone and amoxicillin.

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 hematological or solid malignancy.

This prospective multicentre cohort data from 2 centers in Melbourne (Australia) support the safety of *in vivo* testing for severe T-cell-mediated hypersensitivity, including SCAR.³ These data are 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. Although IDT has been performed sporadically for decades,^{11,12} it is frequently avoided outside of Europe because

of lack of availability of sterile, pharmacy-prepared, and Food and Drug Administration–approved reagents for IDT and concerns of systemic adverse reactions, especially among ICHs 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 are always required. However, the morbidity and potential opportunities for medication errors after severe T-cell-mediated hypersensitivity without a clear label is also evident.

Although 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 reactions.¹⁵ These data despite their limitations support the safety of skin testing, especially in our most vulnerable patients such as ICHs. It should prompt new guidelines to support the use of skin testing, in particular IDT for DRESS or nonspecific exanthems in carefully selected patients.

^aDepartment of Infectious Diseases and Centre for Antibiotic Allergy and Research, Austin Health, VIC, Heidelberg, Australia

^bDepartment of Infectious Diseases, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

^cDepartment of Medicine (Austin Health), University of Melbourne, Heidelberg, VIC, Australia

^dThe National Centre for Infections in Cancer, Department of Infectious Diseases, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

^eDepartment of Dermatology, Austin Health, Heidelberg, VIC, Australia

^fDepartment of Dermatology, Alfred Health, Heidelberg, VIC, Australia

^gInstitute for Immunology and Infectious Diseases, Murdoch University, Murdoch, WA, Australia

^hDepartment of Medicine, Vanderbilt University Medical Centre, Nashville, Tenn

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Corresponding author: Jason A. Trubiano, MBBS, PhD, Austin Health, Centre for Antibiotic Allergy and Research, Department of Infectious Diseases, Austin Hospital, 145 Studley Rd, Heidelberg, VIC 3084, Australia. E-mail: jason.trubiano@austin.org.au.

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TABLE E1. Concentrations used for IDT and PT

Drug	Intradermal concentration (mg/mL)	Patch concentration (%)
Amoxicillin	20	10
Amoxicillin clavulanate	NA	10
Ampicillin	25	10
Benzylpenicillin	1, 10	NA
Cefazolin	1	NA
Cephalexin	NA	0.5
Ceftriaxone	1	10
Cefepime	1	NA
Ciprofloxacin*	0.05, 0.125	10
Clindamycin	15	NA
Flucloxacillin	2	NA
Meropenem	2.5	NA
Metronidazole	3	0.75
Piperacillin-tazobactam	3 (piperacillin)	NA
Diater DAP - PPL (benzylpenicilloyl poly-L-lysine—the major determinant)	Neat	NA
Diater DAP - MDM (benzylpenicilloate)	Neat	NA
Sulfamethoxazole	NA	10
Trimethoprim	NA	5
Vancomycin*	0.5, 5	0.05, 0.5

MDM, Minor determinant mixture; NA, not applicable/available; PPL, penicilloyl polylysine.

*A potentially higher concentration was used, because immediate mast-cell–related responses known to be associated with these drugs were irrelevant to the investigated delayed (6–48 h) intradermal T-cell–mediated response.