

Received for publication February 21, 2019; accepted for publication February 21, 2019.
Corresponding author: Gillian E. Caughey, PhD, Discipline of Pharmacology,
Adelaide Medical School, University of Adelaide, North Tce, Adelaide, SA
5001, Australia. E-mail: gillian.caughey@adelaide.edu.au.

REFERENCES

1. Devchand M, Urbancic KF, Khumra S, Douglas AP, Smibert O, Cohen E, et al. Pathways to improved antibiotic allergy and antimicrobial stewardship practice: the validation of a beta-lactam antibiotic allergy assessment tool. *J Allergy Clin Immunol Pract* 2019;7:1063-5.e5.
2. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. *JAMA* 2019;321:188-99.
3. Barlam TF, Fishman NO, Hamilton CW, Jenkins TC, Lipsett PA, Malani PN, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis* 2016;62:e51-77.
4. van Dijk SM, Gardarsdottir H, Wassenberg MWM, Oosterheert JJ, de Groot MCH, Rockmann H. The high impact of penicillin allergy registration in hospitalized patients. *J Allergy Clin Immunol Pract* 2016;4:926-31.
5. Macy E. Penicillin and beta-lactam allergy: epidemiology and diagnosis. *Curr Allergy Asthma Rep* 2014;14:476.
6. Inglis JM, Caughey GE, Smith W, Shakib S. Documentation of penicillin adverse drug reactions in electronic health records: inconsistent use of allergy and intolerance labels. *Intern Med J* 2017;47:1292-7.
7. Chen JR, Tarver SA, Alvarez KS, Tran T, Khan DA. A proactive approach to penicillin allergy testing in hospitalized patients. *J Allergy Clin Immunol Pract* 2017;5:686-93.

<https://doi.org/10.1016/j.jaip.2019.02.046>

Reply



To the Editor:

We read with the interest the correspondence by Caughey et al¹ regarding the recently published antibiotic allergy assessment tool (AAAT).² We agree that external validation is required for widespread implementation and strongly encourage the practice undertaken by the authors. Caughey et al have demonstrated the efficacy of the AAAT to detect intolerances, which arguably should not be reported in the “allergy” electronic medical record (EMR), when matched against the EMR allergy documentation alone. The application of the tool to a database that only includes the EMR of the adverse drug reaction (ADR) and without active reconciliation of the patients’ ADRs by a trained professional is not how the AAAT was initially designed or internally validated. This is important considering that 25% to 30% of allergies in the EMR are incorrect and a significant proportion incomplete or “unknown.”^{3,4} This tool was designed and validated to enable health care providers obtain an accurate and prospective β -lactam allergy assessment after patient interview/case scenario, subsequently improving the accuracy of the EMR. The authors highlighted the large proportion ($n = 1980$) of EMRs stating “rash with no other information” and “unknown/uncertain timing” ($n = 1017$). However, we suspect that the vast majority of these reactions, after correct application of the AAAT at the bedside, could have been more appropriately classified as “low risk.” The collective low-risk phenotypes of (1) unknown reaction, (2) rash >10 years previously, and (3) childhood rash account for greater than 50% of reported antibiotic allergies, extrapolating from an interviewed inpatient population with antibiotic allergies.³ The AAAT was recently applied to a real-world scenario, in an Antimicrobial Stewardship (AMS)-led penicillin allergy ward round, resulting in 40% of inpatients with a penicillin allergy being considered “low risk.”⁵ Although point-of-

care “delabeling” is the optimal way of reducing the burden of penicillin allergies, tools such as the AAAT are most likely to be used by nonallergists; therefore, they need to ensure safety.

The discussion around health care utilization and avoiding costly and labor-intensive skin testing, which in the most part is currently unavailable to most stakeholders,⁶ is timely. Clearly, this is not feasible with a projected 2 million Australians and over 30 million North Americans reporting a penicillin allergy.⁷ However, assessment tools should endeavor to enable a larger skilled health care proportion to directly delabel and/or oral challenge patients with validated “low-risk” allergies. As authors correctly suggest, patients identified with a “moderate-risk” allergy are likely to be referred to testing services. We suggest that testing services should specifically prioritize patients with immediate and/or ongoing antibiotic needs, which reflects our practice as demonstrated in a previously published outpatient-tested cohort where 48% were immunocompromised.⁸ The development of multidisciplinary models of care,⁹ engagement of a pharmacist workforce,¹⁰ and improvement of the exposure of fellows in training to drug allergy,¹¹ is likely to help offset the increased demand for testing services. Published antibiotic allergy tools, in addition to aiding assessment, hopefully will provide clinicians with direction around the safety of alternative β -lactam utilization. We hope that the uptake of alternative β -lactams, in particular cephalosporins, occurs in patients with reported low- and moderate-risk allergies, considering the under 2% rate of cross-reactivity.⁹ We look forward to further work to validate a range of β -lactam allergy tools that will improve EMR accuracy, β -lactam utilization, and point-of-care delabeling.

Jason A. Trubiano, MBBS, PhD^{a,b,c,d}
Misha Devchand, BPharm^{a,b}
Elizabeth J. Phillips, MD^{e,f}

^aInfectious Diseases Department and Centre for Antibiotic Allergy and Research, Austin Health, Heidelberg, Victoria, Australia

^bPharmacy Department, Austin Health, Heidelberg, Victoria, Australia

^cNational Centre for Infections in Cancer, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

^dDepartment of Medicine, Austin Health, University of Melbourne, Parkville, Victoria, Australia

^eInstitute for Immunology and Infectious Diseases, Murdoch University, Murdoch, Western Australia, Australia

^fDepartment of Infectious Diseases, Vanderbilt University, Nashville, Tenn.

JAT is supported by a National Health and Medical Research Council Early Career Fellowship (GNT1139902), and also by a postgraduate scholarship from The National Centre for Infections in Cancer, Peter MacCallum Cancer Center, Australia. EJP is supported in part by the National Institutes of Health (NIH) (award numbers 1P50GM115305-01 and 1R01AI103348-01), the NIH-funded Tennessee Center for AIDS Research (P30 AI110527), 1R13 AR071267-01, NHMRC, ACH2, and the Angela Anderson Foundation.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication February 23, 2019; accepted for publication February 28, 2019.
Corresponding author: Jason A. Trubiano, MBBS, PhD, Austin Health, 145 Studley Road, Heidelberg, VIC 3084, Australia. E-mail: jason.trubiano@austin.org.au.

REFERENCES

1. Caughey GE, Shakib S, Inglis JM, Le T-T, Yuson CL, Smith WB. External validation of beta-lactam antibiotic allergy assessment tools: implications for clinical practice and workforce capacity. *J Allergy Clin Immunol Pract* 2019;7:2094-5.
2. Devchand M, Urbancic K, Khumra S, Douglas AP, Smibert O, Cohen E, et al. Pathways to improved antibiotic allergy and antimicrobial stewardship practice—the validation of a beta-lactam antibiotic allergy assessment tool. *J Allergy Clin Immunol Pract* 2019;7:1063-5.e5.

3. Trubiano JA, Pai Mangalore R, Baey YW, Le D, Graudins LV, Charles PG, et al. Old but not forgotten: Antibiotic allergies in General Medicine (the AGM Study). *Med J Aust* 2016;204:273.
4. Moskow JM, Cook N, Champion-Lippmann C, Amofah SA, Garcia AS. Identifying opportunities in EHR to improve the quality of antibiotic allergy data. *J Am Med Inform Assoc* 2016;23:e108-12.
5. Devchand M, Kirckpatrick C, Stevenson W, Garrett K, Perera D, Khumra S, et al. Evaluation of a pharmacist-led penicillin allergy de-labelling ward-round—a novel antimicrobial stewardship intervention. *J Antimicrob Chemother* 2019;74:1725-30.
6. Trubiano JA, Beekmann SE, Worth LJ, Polgreen M, Thursky KA, Slavin MA, et al. Improving antimicrobial stewardship by antibiotic allergy delabeling: evaluation of knowledge, attitude, and practices throughout the emerging infections network. *Open Forum Infect Dis* 2016;3:ofw153.
7. Trubiano JA, Adkinson NF, Phillips EJ. Penicillin allergy is not necessarily forever. *JAMA* 2017;318:82-3.
8. Trubiano JA, Thursky KA, Stewardson AJ, Urbancic K, Worth LJ, Jackson C, et al. Impact of an integrated antibiotic allergy testing program on antimicrobial stewardship: a multicenter evaluation. *Clin Infect Dis* 2017;65:166-74.
9. Trubiano JA, Stone CA, Grayson ML, Urbancic K, Slavin MA, Thursky KA, et al. The 3 Cs of antibiotic allergy-classification, cross-reactivity, and collaboration. *J Allergy Clin Immunol Pract* 2017;5:1532-42.
10. Cheon E, Horowitz HW. New avenues for antimicrobial stewardship: the case for penicillin skin testing by pharmacists. *Clin Infect Dis* 2019;68:2123-4.
11. Derrick MI, Williams KB, Shade LMP, Phillips EJ. A survey of drug allergy training opportunities in the United States. *J Allergy Clin Immunol Pract* 2018;6:302-4.

<https://doi.org/10.1016/j.jaip.2019.02.047>

Tissue compression and epinephrine deposition



To the Editor:

In his editorial “Epinephrine needle length in autoinjectors and why it matters” in the *Journal of Allergy and Clinical Immunology: In Practice*, Song¹ reviewed the findings of Duvauchelle et al,² reporting new data on the pharmacokinetics of epinephrine and epinephrine autoinjectors (EAI). We disagree with a number of Song’s interpretations of earlier studies.

First, Song claims that when using an EAI, epinephrine is not deposited at the tip of the needle but forced further by high pressure. This finding is from a pig model study where there was no assessment of the impact of muscle fascia. Importantly, Diacono et al³ found that the propulsive force of autoinjectors did not propel the epinephrine through the fascia using a pig model. We agree with the data by Diacono et al suggesting that the needle must pass through the whole muscle fascia and the epimysium to deliver epinephrine into muscle (IM).

Secondly, Song claims that the subcutaneous (SC) tissue is compressed by the injection pressure from autoinjectors. It is true that some compression of SC tissue occurs. But on average only 10% of the compression is in the SC tissue and approximately 90% of the compression takes place in the muscle⁴ (Table I). So compression has a relatively small impact on successful IM delivery. The SC tissue is more compressed in women than in men.

Thirdly, Song¹ claims that “It is likely that the propulsive force may be sufficient in some instances to propel epinephrine across the fascia into the IM space” without providing any evidence. We do not believe that EAI given SC will deliver the drug intramuscularly. Song cites Diacono et al,³ who identified that the epinephrine jet does not penetrate the fascia. However, Song

TABLE I. New data from the original papers analyzing STMD, STBD min and max and % compression of the subcutaneous tissue in adult women (n = 67) and men (n = 32)

Variable	n	Mean	Min	Max	Significances
STMD _{min} women	67	15.4	6.0	31.7	<.000001 Women STMD _{min} vs STMD _{max}
STMD _{min} men	32	6.9	3.3	13.6	
STMD _{max} women	67	12.9	5.0	27.7	<.000001 P ≤ .000001 Men STMD _{min} vs STMD _{max}
STMD _{max} men	32	6.3	2.7	13.7	
Compression SC % women	67	15.8	−9.5	48.8	<.000001 P ≤ .000001
Compression SC % men	32	3.2	−1.8	13.0	

SC, Subcutaneous; STMD, skin to muscle distance; STBD, skin to bone distance. *t*-tests were performed.

did not use Diacono et al’s findings when stating his claims. Furthermore, in Duvauchelle et al’s study,² imaging of SC injections does not appear to lead to ultrasound changes in the IM compartment. This suggests that the SC epinephrine did not penetrate into muscle.

Lastly, Song claims that estrogens may influence the pharmacokinetics of epinephrine when assessed in these studies that span several minutes only. We cannot rationalize how estrogen would impact epinephrine levels in such studies. We could not find any evidence in the medical literature to support this idea.

We conclude that until further human experiments have been performed, the pig model data showing that epinephrine is not forced through the fascia by the high jet pressure should be accepted, that the compression of the SC tissue by EAI is limited, and that there seems to be little difference in tissue compression between men and women.

Sten Dreborg drafted the correspondence and Harold Kim and Sten Dreborg reviewed the text critically and accepted the final version.

Sten Dreborg, MD, PhD^a
Harold Kim, MD^{b,c}

^aDepartment of Child and Adolescent Allergology, Women’s and Children’s Health, Uppsala University, Uppsala, Sweden

^bDivision of Clinical Immunology and Allergy, Western University, London, Ontario, Canada

^cMcMaster University, Hamilton, Ontario, Canada.

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest. Received for publication February 23, 2019; accepted for publication March 27, 2019.

Corresponding author: Sten Dreborg, MD, PhD, Department of Child and Adolescent Allergology, Women’s and Children’s Health, Uppsala University, Uppsala SE-75185, Sweden. E-mail: sten.dreborg@kbh.uu.se.

REFERENCES

1. Song TT. Epinephrine needle length in autoinjectors and why it matters. *J Allergy Clin Immunol Pract* 2018;6:1264-5.
2. Duvauchelle T, Robert P, Donazzolo Y, Loyau S, Orlandini B, Leheret P, et al. Bioavailability and cardiovascular effects of adrenaline administered by anapen autoinjector in healthy volunteers. *J Allergy Clin Immunol Pract* 2018;6:1257-63.