

Beta-Lactam and Sulfonamide Allergy Testing Should Be a Standard of Care in Immunocompromised Hosts



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Antibiotic allergies are reported in up to 1 in 4 immunocompromised hosts with significant impacts on antibiotic utilization and patient outcomes. Health services programs focused on de-labeling beta-lactam and sulfonamide allergy labels should be a standard of care in immunocompromised hosts. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2151-3)

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INTRODUCTION

The increasing threat of antimicrobial resistance continues to drive development of novel programs to improve the appropriate use of antibiotics and aid antimicrobial stewardship.^{1,2} The high prevalence of patient-reported antibiotic allergies (so-called antibiotic allergy labels [AALs]),³⁻⁵ in particular penicillin allergies, in combination with the known associations between

AALs and antimicrobial resistance,^{6,7} has driven calls for antibiotic allergy “de-labeling” to be a standard fixture of antimicrobial stewardship programs.^{1,2} This is particularly relevant for high-antibiotic usage populations,⁸ such as immunocompromised hosts and those with pending immunosuppression where the prevalence of AALs is highest and so is the rate of broad-spectrum antibiotic utilization and antimicrobial resistance.⁹ Although antibiotic allergy testing has demonstrated that more than 85% of patients can be delabeled with skin testing followed by oral provocation,^{10,11} the utility of antibiotic allergy testing in different populations of immunologically altered hosts has until recently been ill defined and supportive data absent. Frequently, this cohort of patients had been excluded from antibiotic allergy testing studies despite being the group most likely to benefit from appropriate antibiotic options.

The prevalence of AALs has frequently been demonstrated to be highest in immunocompromised hosts, up to 35.1% in 2 tertiary referral hospitals in the United States (2010-2015).¹² In addition, we reported an AAL prevalence of 24% in a cohort of Australian cancer patients admitted with an infective episode between 2013 and 2014 to a stand-alone cancer hospital.¹³ Both the Australian and US studies demonstrated significant health care AAL impacts, including higher readmission rates, increased utilization of restricted antibiotics, and longer antibiotic course duration.^{12,14} The combination of high prevalence and associated inferior hospital outcomes should focus our attention on this group for targeted testing and delabeling programs, in particular before planned immunosuppression.¹⁵

Antibiotic prophylaxis strategies are severely hampered by the reported presence of both penicillin and “sulfa” allergies, which also happen to be the 2 most common AALs globally. Penicillins are the preferred prophylaxis strategy to prevent infection with encapsulated organisms in asplenia¹⁶ and allogeneic bone marrow transplantation.¹⁷ Identification of penicillin-allergic individuals should trigger referrals to antibiotic allergy testing programs to enable prophylaxis with penicillin family drugs. In the setting of a confirmed penicillin hypersensitivity, desensitization is an appropriate tool to use particularly when long-term uninterrupted dosing of penicillins is indicated. For patients reporting a nonsulfonamide allergy, there is no cross-reactivity with antibiotic sulfonamides; hence, trimethoprim-sulfamethoxazole (TMP-SMX) should be used in these patients reporting “sulfur” allergy.¹⁸ In those with a historical antibiotic-sulfonamide allergy, oral rechallenge should be performed via a 2-step challenge (TMP-SMX; 8 mg/40 mg followed by 72 mg/360 mg) or a single-step challenge (TMP-SMX, 80 mg/400 mg), for mild

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Abbreviations used

AAL- Antibiotic allergy label

TMP-SMX- Trimethoprim-sulfamethoxazole

immediate hypersensitivities or mild delayed hypersensitivities, respectively. This protocol was successfully used in a total of 46 immunocompromised patients without any adverse event in the North America¹⁹ and Australia.²⁰ In those with confirmed antibiotic-sulfonamide cross-reactivity, dapson despite being an antibiotic sulfonamide can be used in most instances due to the low rate of cross-reactivity (9%-13%).²¹ A step-wise approach to alternatives in the setting of moderate to severe antibiotic-sulfonamide allergy is available to clinicians.^{20,22}

We have demonstrated the benefits of antibiotic allergy testing, primarily for beta-lactam and sulfonamide AALs, to the immunocompromised host. In a multicenter study of 118 patients with AAL undergoing protocolized antibiotic allergy testing, of which 48% (n = 57) were immunocompromised, 84% were “de-labeled” and a resultant 12-fold increase in antibiotic appropriateness was observed.²³ In this study, immunocompromised was defined as hematological malignancy, oncological malignancy, solid-organ or stem cell transplant recipient, autoimmune disease, condition requiring more than 15 mg steroid daily for 1 month. This study examined patients reporting any antibiotic allergy, predominantly penicillins (54.4%), cephalosporins (18.1%), and sulfonamide antibiotics (7.5%). This finding was further validated in a cohort of 59 cancer patients with a similar AAL distribution, in whom no adverse events from testing were reported and a 4-fold increase in appropriate prescribing and 21-fold increase in preferred beta-lactam/beta-lactamase prescribing was noted.¹³ A recent study by Taremi et al²⁴ adds to the published literature already supporting penicillin allergy testing in the immunocompromised host, and demonstrates a 95% delabeling rate and posttesting utilization of penicillins in 51%.²⁴ This collective work demonstrates that

antibiotic allergy testing, in particular for beta-lactams, is both safe and effective in immunocompromised hosts. The question for clinicians caring for immunocompromised hosts should no longer be whether they offer testing to their patients but how such testing can be incorporated into the care plans of such patients.

If we are to implement antibiotic allergy testing into the routine care of the immunocompromised host, risk-stratification is required to determine who can move to direct oral provocation and who requires initial skin testing. In hematological malignancies and stem cell transplantation, there is an increased rate of maculopapular exanthema,^{12,25} potentially related to a drug allergy “mimicker” (eg, engraftment syndrome, viral infection, and skin graft vs host disease), and these should be actively pursued to potentially allow direct delabeling in patients in whom an alternative diagnosis is established. There is growing literature to support the safe use of direct oral rechallenge in those who are identified as low-risk—childhood exanthema, unknown reactions, family history, pruritus without rash.^{15,26-28} This may be particularly useful when identifying patients before the initiation of immunosuppressive therapy. Although data are primarily from the outpatient and pediatric setting, there is no current evidence to indicate that an immunocompromised hospitalized patient should be managed differently. This is supported by our pilot work, where the implementation of a low-risk criteria allowed the safe oral challenge in 48 patients, including cancer patients.²⁹ In patients of moderate or high risk (eg, anaphylaxis or immediate symptoms to suggest IgE-mediated hypersensitivity), antibiotic allergy testing such as prick and intradermal testing can be performed safely in this cohort.²³ There are emerging data to support the role of patch and delayed intradermal skin testing in severe cutaneous adverse drug reactions in any host; however, reassuringly there are emerging data that even performing this “higher risk” testing in immunocompromised hosts is safe and improves beta-lactam utilization.³⁰ Although immunosuppression has the theoretical potential to cause a “false-negative” skin prick or intradermal test result primarily in delayed testing, in our tested cohorts we did not see adverse events to previously

Beta-lactam and Sulfonamide Allergy Testing in the Immunocompromised Host

Primary Focus: Identify patients with likely increase risk of infective complication - solid organ or bone marrow transplant (pre or post), haematological malignancy, oncological malignancy, splenectomy, previous/future high-dose steroid therapy (> 15mg daily for 1 month) and patients pre chemotherapy or other immunosuppression (e.g. autoimmune/connective tissue disorder)

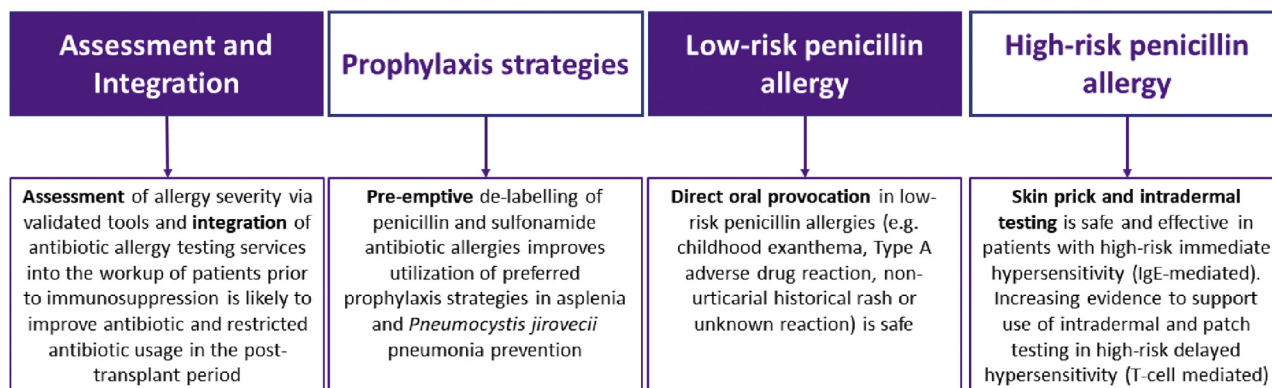


FIGURE 1. Key points to approaching antibiotic allergy in the immunocompromised host.^{15,19,20,23,24,29-31}

delabeled antibiotics in the 90-day posttest period.^{13,23,29} It is also relevant that these populations are complex and in many their immune system may not normalize either due to their associated therapies or underlying immune dysregulation, so it becomes a practical issue of being able to provide them clear guidance for future safe antibiotic options. Indeed, the vast majority of them who are labeled as allergic to beta-lactam or sulfa antibiotics at the time of their initial diagnosis would have tested negative before the onset of immunocompromising therapy. We recommend that prednisone therapy be at the lowest manageable dose at the time of testing where feasible. To avoid this issue, ideally wherever possible, patients before immunosuppression should be referred and appropriately evaluated. Although larger cohort studies are required to demonstrate the safety of risk-stratified antibiotic allergy testing in immunocompromised hosts, the current body of evidence suggests that such testing is feasible and efficacious.

The immunocompromised host is an emerging cohort with heightened antibiotic needs compounded by a large AAL burden. The AAL, in particular toward penicillin, can no longer be ignored and the key targets need addressing (Figure 1). The result of attending to AALs in immunocompromised hosts is improved antibiotic appropriateness. Future work is required to determine the direct benefit to patient efficacy and safety and health economic and antimicrobial resistance benefits of antibiotic allergy testing in this cohort and ways in which risk-stratification can afford access to testing for more patients. However, for now, clinicians caring for this cohort should be asking if their patients are “truly” allergic to antibiotics and how they can proactively be “de-labeled.”

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