

Characteristics and Prevalence of Antibiotic Allergies in Patients with Sickle Cell Disease: A Single Center Retrospective Study

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To the Editor:

Sickle cell disease (SCD) is a group of inherited hemoglobinopathies associated with functional asplenia which results in increased risk for invasive bacterial infections due to encapsulated organisms, *Staphylococcus aureus*, and enteric pathogens. Penicillin prophylaxis is recommended in children with SCD age 5 years and younger to reduce pneumococcal infections. Additionally, bacterial infection is a common cause of hospitalization and death in adults with SCD. Prompt antibiotic therapy, typically using a third-generation cephalosporin, during fever is crucial.¹

Greater rates of reported adverse reactions to antibiotics have been found in patients with increased risk of bacterial infections (e.g. cystic fibrosis², solid organ and hematopoietic cell transplant recipients³) and in patients who have chronic inflammatory conditions (e.g. systemic lupus erythematosus, spondyloarthritis, and rheumatoid arthritis).⁴ We hypothesize that SCD, a condition associated with greater risk of bacterial infections and chronic inflammation, may be associated with increased prevalence of antibiotic allergies. However, there is a literature gap concerning the prevalence and characteristics of antibiotic-associated adverse reactions in patients with SCD. We aimed to characterize adverse antibiotic reactions and identify rates of allergy referral in this population. We conducted a retrospective review in May 2021 to identify patients with SCD with antibiotic allergy labels (i.e., any antibiotic listed in allergy section of the electronic medical record [EMR]).

Patients with a diagnosis of SCD (i.e., homozygous SCD, sickle-beta thalassemia, and HbSC disease) aged 0-100 years with documented allergies to antibiotics who sought care at our

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institution between 2011-2021 were included. Patients were identified by ICD-10 codes for sickle cell disorders (D57.0-D57.8) and confirmed by chart review. Sickle cell trait diagnosis was excluded based on ICD-10 code (D57.3) or chart review. To ensure that the allergy documentation was current, only patients whose allergy lists were reviewed by a provider between 2019-2021 were included. Data including age, sex, antibiotic allergies, referrals, laboratory and skin testing for antibiotic allergies, and antibiotic oral challenges were collected. Reactions listed in the allergy section of the EMR and description of reactions in provider notes were extracted. Antibiotic reactions were classified as immediate-type (e.g. hives, angioedema, and/or anaphylaxis occurring within 2 hours of exposure), side effect/intolerance (e.g. headache, gastrointestinal symptoms), pseudoallergy (e.g. vancomycin infusion reaction), nonspecific cutaneous reaction (e.g. reactions reported as “rash” without additional information in EMR, maculopapular exanthems occurring ≥ 6 hours after exposure), or unknown (i.e., reactions with insufficient documentation). This study was approved by the Yale University Institutional Review Board (No. 2000030388).

We identified 740 patients with SCD seen at our institution between 2011-2021. In total, 87 of 740 patients (12%) had ≥ 1 antibiotic allergy label. The median age was 31 years (range 7-85 years), and 64% were female. Twenty-seven of 87 (31%) had >1 antibiotic allergy label. Of these 27 patients, the average number of antibiotic allergy labels was 2.7 (range 2-7).

Of the 132 adverse reactions reported, penicillins (37%; 49/132), cephalosporins (22%; 29/132), and sulfonamides (11%; 15/132) were most commonly implicated (Table 1). Most documented reactions were immediate-type (51%; 67/132), nonspecific cutaneous reactions (21%; 28/132), or

unknown (18%; 24/132). Side effects or intolerances accounted for 6% (8/132) of reactions.

Only 6 of 87 (7%) patients were referred to evaluate drug allergy. Of these 6 patients, 2 had an allergy consultation (1 inpatient, 1 outpatient), 2 did not schedule an appointment, and 2 no-showed to their appointments. One patient underwent skin testing and passed a penicillin oral challenge.

We found that 12% of patients with SCD had ≥ 1 antibiotic allergy label; this prevalence is consistent with prior studies in a general population, which have estimated that 10-15% of United States patients carry an antibiotic allergy label.⁵ Interestingly, we found that 39% (52/132) of these reactions were nonspecific cutaneous reactions or not specified in the EMR. Given the literature on antibiotic allergy delabeling and true prevalence in the general population, we strongly suspect that the documented antibiotic allergies do not accurately reflect true drug hypersensitivities requiring avoidance in this patient population.⁵ Further allergy evaluation of the immediate-type reactions (51%; 67/132) may potentially result in delabeling. Patients reporting side effects or intolerances may be safely reintroduced following allergy evaluation. Unfortunately, only 7% of the patients identified in our cohort have had an allergy referral. These findings highlight the need for more stringent allergy documentation and referrals for those labeled with antibiotic hypersensitivities in order to progress antibiotic stewardship.

Another important finding revealed that 59% (78/132) of the antibiotic allergy labels were to beta-lactams, which are common empiric antibiotics for infections associated with SCD and functional asplenia (Table 1).¹ None of the patients with a penicillin allergy label qualified for penicillin prophylaxis based on their age. Our penicillin allergy label prevalence (5.9%; 44/740)

was surprisingly below that of the general population, previously reported to be 10%.⁵ Given the actual prevalence of true penicillin allergy in the general population (<5%), further evaluation could likely result in successful delabeling.⁵

Even with true IgE-mediated beta-lactam hypersensitivity, patients are likely to spontaneously lose the allergy after 5-10 years.⁵ Notably, the prevalence of reported cephalosporin allergy (3%; 23/740) was higher than prior studies, estimated to be 1-2% in the general population.⁵ Beta-lactam allergy may result in suboptimal antibiotic therapy and unnecessary exposure to broad-spectrum antibiotics during treatment of infections associated with SCD. Efforts to delabel antibiotic allergy labels in this population should be a key component of antibiotic stewardship initiatives.

Several limitations were identified in our study. Documented reactions in the EMR are limited and potentially inaccurate. Significant discrepancies between patient-reported and allergy documentation have been shown in minority populations.⁶ Given well-established health inequities associated with SCD, greater attention should be given to verification and accuracy of allergy documentation. Additionally, this study is retrospective, limited to a single center, and may not capture all allergy referrals completed outside of our center's EMR.

Disappointingly, we identified a low number of allergy referrals despite an increased antibiotic need in patients with SCD. Our referral rate for antibiotic allergies is comparable to rates seen in other urban adult and pediatric general clinics, 6% and 1.9% respectively.^{7,8} Future quality improvement initiatives will be crucial to identify barriers to allergy referral and evaluation; in

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particular, patients with SCD have decreased access to subspecialty care.⁹ Multicenter or prospective studies which better evaluate the prevalence of antibiotic allergies in this at-risk population are warranted. Lastly, it will be important to understand the clinical outcomes of patients with SCD and antibiotic allergy labels.

To our knowledge, this is the first study to characterize reported antibiotic allergies in patients with SCD. Surprisingly, despite frequent antibiotic exposures in patients with SCD, we found that the prevalence of reported antibiotic allergy in patients with SCD at our institution (12%) is similar to estimates in the general population (10-15%). Moreover, the majority of the reactions were to beta-lactam antibiotics which are first-line antimicrobials for prevention of and management of bacterial infections in patients with SCD. This lower rate may be due to several factors including more diligent antibiotic stewardship by hematologists. It is also important to consider that since penicillin is regularly used as a daily medication in patients with SCD, this finding may also be due to desensitization and an induced immune tolerance.¹⁰ Or more simply, benign rashes like viral exanthems are less likely to be attributed penicillin when taken daily.

Many reported allergies in the general population, especially to penicillin, have been successfully ruled out with proper evaluation. Given frequent antibiotic use and need for antibiotic stewardship in this population, this study highlights the need for better understanding of antibiotic allergies in patients with SCD and for implementation of strategies in SCD care to assess and remove unnecessary antibiotic allergy labels.

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Table 1. Antibiotic allergy labels based on reaction type and antibiotic class.^a

Antibiotic Class	Immediate type (n=67) (%)	Pseudoallergy (n=5) (%)	Side effect/Intolerance (n=8) (%)	Nonspecific cutaneous reactions (n=28) (%)	Unknown (n=24) (%)	Total reactions documented, n (%) (n=132)
Penicillins	23 (34.3)	0	1 (12.5)	17 (60.7)	8 (33.3)	49 (37.1)
Cephalosporin, total	18 (26.9)	0	0	3 (10.7)	8 (33.3)	29 (22.0)
First generation	2 (3.0)	0	0	1 (3.6)	1 (4.2)	4 (3.0)
Second generation	1 (1.5)	0	0	0	1 (4.2)	2 (1.5)
Third Generation	12 (17.9)	0	0	1 (3.6)	3 (12.5)	16 (12.1)
Fourth Generation	0	0	0	1 (3.6)	1 (4.2)	2 (1.5)
Generation not specified	3 (4.5)	0	0	0	2 (8.3)	5 (3.8)
Sulfonamides	2 (3.0)	0	2 (25)	6 (21.4)	4 (16.7)	14 (10.6)
Glycopeptides	6 (9.0)	5 (100)	0	0	2 (4.1)	13 (9.8)
Macrolides	7 (10.4)	0	2 (25)	2 (7.1)	0	11 (8.3)
Tetracyclines	4 (6.0)	0	1 (12.5)	0	0	5 (3.8)
Fluoroquinolones	2 (3.0)	0	1 (12.5)	0	2 (8.3)	5 (3.8)
Lincosamides	2 (3.0)	0	0	0	0	2 (1.5)
Clavulanic acid	2 (3.0)	0	0	0	0	2 (1.5)
Nitrofurantoin	0	0	1 (12.5)	0	0	1 (0.8)
Polytrim B/trimethoprim	1 (1.5)	0	0	0	0	1 (0.8)

^a Of note, no severe IgE-mediated hypersensitivity reactions such as drug rash with eosinophilia and systemic symptoms (DRESS) or Stevens-Johnson syndrome (SJS) were identified.