Vancomycin was first isolated in 1957 from the bacteria *Amycolatopsis orientalis* from the jungles of Borneo. Its name is derived from the word “vanquish.” It is a bactericidal tricyclic glycopeptide active against gram-positive aerobic cocci and bacilli through inhibition of cell wall synthesis. In addition to being first-line therapy for methicillin-resistant *Staphylococcus* infections, it is used as second-line antimicrobial therapy in patients labeled allergic to beta-lactam antimicrobials. Vancomycin is also active against gram-positive anaerobes including *Clostridium difficile*. With vancomycin resistance limited to only a handful of strains, it is one of the most used antimicrobials in the United States.

Hypersensitivity reactions (HSRs) to vancomycin were reported as early as 1962. Most immediate HSRs do not appear to be IgE-mediated. Only 10% of HSR case reports suggest a possible IgE-mediated mechanism based on a convincing clinical presentation, positive skin testing (ST) result, and breakthrough symptoms despite premedication or during desensitization. This may be an overestimation because (severe) red man syndrome (RMS) can be clinically difficult to distinguish from IgE-mediated anaphylaxis. IgE-independent mast cell and basophil degranulation, causing RMS, occurs in up to 47% of patients treated with vancomycin. RMS is mediated through the MAS-related G-protein—coupled receptor X2 and does not require prior sensitizing vancomycin exposure. Among pediatric patients, age 2 years or more, previous RMS, vancomycin doses greater than or equal to 10 mg/kg, and concentrations greater than or equal to 5 mg/mL have been identified as risk factors for developing RMS.

The clinical characteristics of IgE-mediated and IgE-independent vancomycin HSRs can be indistinguishable, and uncertainty remains whether serum mast cell tryptase and ST can act as differentiators. Establishing the underlying mechanism is important because management options differ. Unlike IgE-dependent HSRs, vancomycin can be readministered following RMS, with precautions including premedication and slower infusion rates. Vancomycin desensitization in patients with IgE-mediated vancomycin HSRs should be considered if there are no antimicrobial alternatives and following a careful risk-benefit assessment. Successful intravenous desensitization protocols, both rapid and slow, have been published. Most require premedication and have been associated with mild symptoms such as pruritus; slow protocols are usually used after failed rapid desensitization attempts. Oral and inhaled routes of desensitization have also been described. Desensitization is contraindicated in patients with severe cutaneous adverse reactions (SCARs) (Figure 1).

Although vancomycin-induced nonimmediate HSRs occur less frequently, vancomycin does account for up to two-thirds of antibiotic-associated drug rash eosinophilia and systemic symptoms syndrome (DRESS). Other nonimmediate vancomycin HSRs include maculopapular rash, linear IgA bullous dermatosis, Stevens-Johnson syndrome/toxic epidermal necrolysis, and less frequently acute generalized exanthematous pustulosis.

Owing to the structural similarities of the glycopeptide antimicrobials, cross-reactivity is possible. However, immunologic cross-reactivity has not been demonstrated, and reports of clinically suspected glycopeptide cross-reactivity, immediate and delayed, are limited. RMS cross-reactivity between vancomycin and teicoplanin is unlikely because teicoplanin does not activate the MAS-related G-protein—coupled receptor X2.

In the current issue, Alvarez-Arango et al explore the prevalence of vancomycin allergy labeling and the challenges associated with identifying, characterizing, and documenting vancomycin HSRs. This large cross-sectional study across 2 US health care systems explored vancomycin HSRs documented in electronic health records over a 2-year period. Of 4,490,618 patients, 0.3% (n = 14,426) had a documented vancomycin drug allergy/hypersensitivity label with 18,761 documented suspected vancomycin HSRs. During the same 2-year period, more vancomycin drug allergy/hypersensitivity labels were added (mean, 253 ± 12) than removed (mean 12 ± 2) per quarter. Of the 18,761 documented suspected vancomycin HSRs, 42% were determined likely immediate and 20% likely nonimmediate on the basis of signs and symptoms documented. Common immediate reaction descriptions included RMS (or words/variations synonymous, n = 1909), hives (n = 1759), itching (n = 1651), flushing (n = 1106), and anaphylaxis (n = 708). The commonest nonimmediate HSR description was rash (n = 3710) followed by DRESS (n = 82) and dermatitis (n = 41). DRESS constituted 60% (82 of 136) of all documented suspected SCARs. Among all documented vancomycin HSRs, 3% (n = 536) offered descriptions suggestive of intolerances or side effects. A further 34% (n = 6440) could not be categorized on the basis of description or lack of description provided.

Vancomycin drug allergy/hypersensitivity labels documented as flushing, rash, hives, itching, and anaphylaxis were not
included in the RMS count. The authors did acknowledge the possibility these 10,051 patients may have also experienced RMS. This highlights a study limitation: there was no allergy or dermatology workup to confirm or refute the presence of true vancomycin hypersensitivity. Therefore, it only provides prevalence data on documented suspected but not documented confirmed vancomycin HSRs. Similarly, the phenotyping conducted by the authors, on the basis of signs and symptoms only, was not validated through specialist workup. Attempts to phenotype HSRs may have been undermined by the lack of information regarding reaction timing. For example, a rash documented without further details was considered nonimmediate from the assumed greater prevalence of maculopapular rashes compared with immediate HSR rashes. Reaction timings form a critical part of allergy history taking, without which misdiagnosis and incorrect determination of phenotype can occur.

Vancomycin-induced DRESS, although rare, accounts for a significant proportion of antibiotic-induced DRESS in literature and of all suspected SCARs identified by Alvarez-Arango et al. Notably, 82.6% (19 of 23) of patients with
RegiSCAR-defined vancomycin-induced DRESS carried HLA-A*32:01, compared with 0% of the matched vancomycin-tolerant controls. If this association can be confirmed in larger and diverse cohorts, this allele may offer a potential means of diagnosing and preventing this potentially life-threatening SCAR.

Alvarez-Arango et al observed vancomycin allergy and HSR labels were added more frequently than removed over the study period. Data regarding the proportion of this cohort referred to an allergist or dermatologist may have provided insight into the infrequent removal of vancomycin allergy labeling. With ambiguity surrounding ST and mast cell tryptase, drug provocation testing (DPT) remains the criterion standard in differentiating between IgE-mediated and IgE-independent HSRs. However, because of the associated risks, DPT is often not performed when ST results are positive or mast cell tryptase levels are raised. Tolerance of vancomycin on DPT with premedication and/or slower infusion rates confirms RMS and permits future use of vancomycin (Figure 1). Where the diagnosis of RMS is not confirmed and documented clearly, clinicians may assume an IgE-mediated mechanism, which can lead to unnecessary vancomycin avoidance. Such antimicrobial avoidance can be associated with significant health care implications including delays in treatment, use of suboptimal antimicrobial therapy, worse health care outcomes, and increased health care costs.

In conclusion, Alvarez-Arango et al illustrate the challenges faced when documenting vancomycin HSRs, partly due to the difficulty in differentiating between the IgE-mediated and RMS phenotypes. At present, apart from potentially high risk and costly DPT, there are no validated tests to confirm RMS and allow for vancomycin readministration. In addition, no allergenic determinants of vancomycin have been identified. Further research focused on epitope mapping and role of MAS-related G-protein–coupled receptor X2 in RMS and HLA-A*32:01 in DRESS might help develop reliable in vitro tests capable of both confirming vancomycin HSR and identifying the underlying mechanism.

REFERENCES