


ing global cooperation will better situate the global economy to rapidly supply vaccines and therapeutics in the future. Such cooperation is not only a matter of social justice, it is also a sound pragmatic response to ending a pandemic in which a virus and its variants easily cross borders. With a globally coordinated strategy, epidemiology, efficacy, and ethics can be fully aligned.

Covid-19 vaccines provide a pathway out of this pandemic, but bold, innovative policies that ensure fast and fair distribution are also critical. The United States

 **An audio interview with Dr. Katz is available at NEJM.org**

has an unusual and urgent opportunity to ensure that Covid-19 vaccines are available to all. As Ursula von der Leyen, president of the European Commission, recently explained: A global pandemic requires a world effort to end it none of us will be safe

until everyone is safe. The Biden administration is well positioned to take a leadership role in this next critical phase.

Vaccinating the world is not only a moral obligation to protect our neighbors, it also serves our self-interest by protecting our security, health, and economy. These goals will not be accomplished by making the world wait for wealthy countries to be vaccinated first. By investing in multilateral partnerships with a sense of shared commitment and employing a global allocation strategy that increases supply and manufacturing, we can meet the urgent challenge of Covid-19, while creating sustainable infrastructures and health systems for the future. Getting the world vaccinated may well be the critical test of our time.

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From the Department of Medicine, Brigham and Women's Hospital (I.T.K., R.W.), Harvard Medical School (I.T.K., R.W., A.M.B.), Massachusetts General Hospital Center for Global Health (I.T.K.), and Ariadne Labs (R.W.) all in Boston; the Harvard Global Health Institute (I.T.K., A.M.B.), and Harvard University (A.M.B.) both in Cambridge, MA; and the Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa (L.-G.B.).

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## Vancomycin Infusion Reaction Moving beyond Red Man Syndrome

Santiago Alvarez-Arango, M.D., S. Michelle Ogunwole, M.D., Thomas D. Sequist, M.D., M.P.H., Caitlin M. Burk, M.D., and Kimberly G. Blumenthal, M.D.

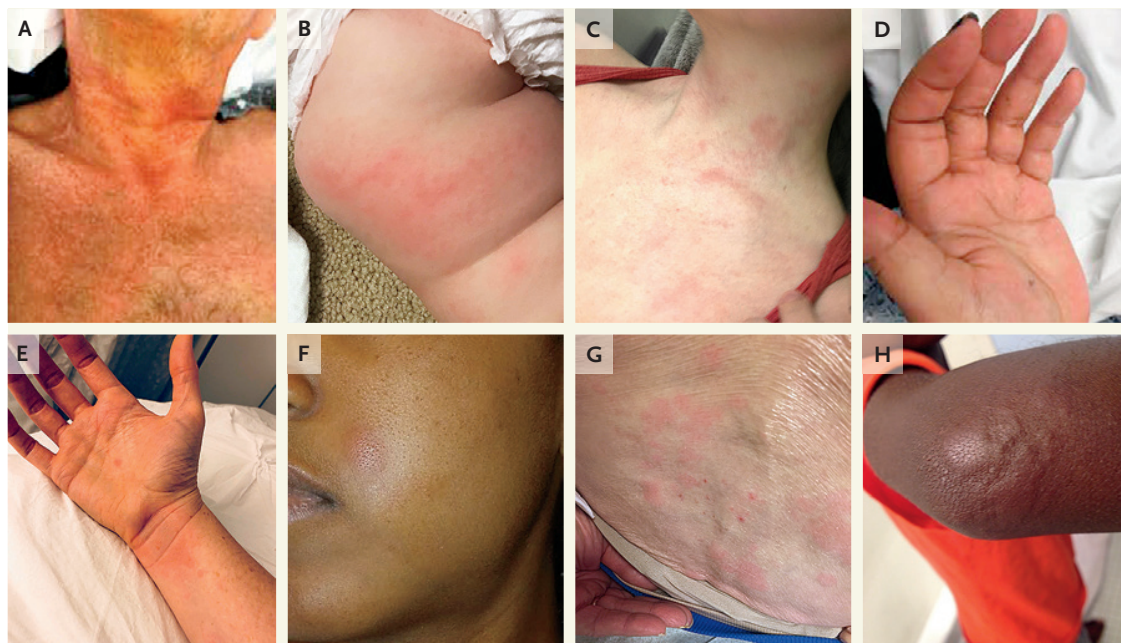
In 1959, an article entitled An Anaphylactoid Reaction to Vancomycin hypothesized that vancomycin-induced histamine release from mast cells had clinical manifestations similar to those of anaphylaxis but less severe. The author named this reaction Red Man Syndrome, reflecting the diffuse erythema in affected patients, and the term caught on in 1985, when the *Journal* published a letter entitled Vancomycin and the Red Man's Syndrome.<sup>1</sup> Although red man might, at first glance, be taken as a straightforward description of a white male patient with an erythematous skin

reaction, the term Red Man had a ready referent outside medicine, where it had long carried racist connotations.

Like redskin, Red Man calls up historical narratives that endorse and reinforce discrimination against Native American and Indigenous peoples. Such narratives were deeply embedded in popular culture: L. Frank Baum, the author of the *Wizard of Oz*, for example, wrote after the massacre at Wounded Knee, With his fall the nobility of the Redskin is extinguished, and what few are left are a pack of whining curs who lick the hand that smites

them. The song What Makes the Red Man Red in the Walt Disney movie of *Peter Pan* depicts Native Americans as animals.<sup>2</sup> Citing this history, some observers have called for replacing the trauma-invoking term,<sup>1</sup> yet Red Man Syndrome continues to be used by clinicians worldwide.

Current use of this term causes inequities beyond its original racist implications: by implying a white male reference, it perpetuates biases and racial norms that may undermine prompt and equitable diagnoses and treatment. Furthermore, its use as a clinical descriptor supports race-based



**Dermatologic Findings in Patients Varying in Age, Sex, and Skin Color.**

The immediate reaction to drugs, including the vancomycin infusion reaction, can present as erythema that can be confluent or blotchy, typically involving the head and neck but also the trunk, extremities, and palms or soles (Panels A through D) or urticaria that can be localized or diffuse (Panels E through H).

medicine, the system by which research characterizing race as an essential, biological variable, translates into clinical practice, leading to inequitable care.<sup>3</sup> And it perpetuates the underrecognition of skin findings in diverse patient populations. We believe it is time to rename this reaction and pursue systemwide improvements in drug-allergy recognition and documentation that are responsive to diverse patient populations.

Because of the increased prevalence of methicillin-resistant *Staphylococcus aureus*, vancomycin is now the most commonly used antibiotic in U.S. hospitals, and without a specific infusion protocol, as many as half of patients who receive it experience symptoms consistent with Red Man Syndrome.<sup>4</sup> Although it is a common reaction documented in electronic health records (EHRs), it is not documented uniformly across patients. In a 2012 retrospective study, White patients were deemed more

likely to experience Red Man Syndrome than non-White patients (odds ratio [OR], 12.5; 95% confidence interval [CI], 1.7 to 90.1).<sup>5</sup> The investigators inferred that Black race was protective against this reaction—a race-based conclusion suggesting that Black patients have different biologic mast-cell responses to vancomycin. The authors failed to consider other potential mechanisms of underdocumentation of Red Man Syndrome in non-White patients.

Recently, we reported findings from a cross-sectional study of patients with a vancomycin allergy documented between 2017 and 2019 in two U.S. health care systems. Because Red Man Syndrome is not a coded reaction entry in EHRs, we used natural language processing to identify its documentation in all its varied free-text permutations. We found that the syndrome was one of the most commonly documented reactions to vancomycin, accounting

for 16% of reactions with classically allergic symptoms. However, among patients with reactions possibly representing the syndrome (some combination of rash, flushing, itching, and hives), Red Man Syndrome was more likely to be specified in documentation for male than for female patients (OR, 1.30; 95% CI, 1.17 to 1.44) and less likely for Black than for White patients (OR, 0.59; 95% CI, 0.47 to 0.75).<sup>4</sup> This slanted application of the term may be attributable to cognitive or implicit biases.

Gender- and race-related bias is problematic for clinical care. The more detailed the drug-allergy documentation in the EHR, the higher the likelihood that a specific drug will be used or not used appropriately in the future.<sup>4</sup> Incomplete documentation can lead to avoidance or to use of alternative agents, which may adversely affect the quality and cost of care.<sup>4</sup> In this case, documented

Red Man Syndrome tells future clinicians that vancomycin is reasonably safe for readministration, as long as the infusion rate is reduced or the patient is pretreated with an antihistamine (or both). Therefore, any patient with documented Red Man Syndrome would probably be retreated with vancomycin if necessary. But patients with documented vancomycin reactions not specified as Red Man Syndrome would probably be perceived as truly allergic, warranting strict avoidance of vancomycin.

It seems likely that the documentation differences we observed affect the timing and choice of the antibiotic administered. For example, a White man with documented Red Man Syndrome might well receive vancomycin again, whereas a Black or female patient with a similar reaction not labeled Red Man Syndrome would probably receive delayed antibiotic treatment with an alternative drug. Since drug allergies are rarely removed from a patient's EHR,<sup>4</sup> a vancomycin allergy is likely to affect a lifetime of clinical decisions.

It is time to rename this reaction using a gender- and race-conscious approach that reinforces, rather than undermines, equitable care delivery. We can move beyond Red Man Syndrome just as we have changed problematic eponyms to avoid Nazi associations or confronted race corrections in clinical practice.<sup>3</sup> This renaming, however, will require substantial work affecting clinical practice, education, and research. We propose the following steps.

First, physicians can stop teaching Red Man Syndrome and stop using it in clinical practice. All language used in clinical medicine should be scrutinized for potential harmful effects. The term

Red Man Syndrome causes harm, which should be enough reason to stop using it. But there is an additional reason: it is not clinically useful because it centers on manifestations in white male patients without considering patients' diversity. Instead, we recommend using the term infusion reaction for all nonimmune-mediated drug reactions; these reactions are typically infusion-rate-dependent and can be prevented with rate changes, premedication (e.g., with antihistamines), or both. This change will also facilitate drug-allergy documentation for other drugs that cause infusion reactions.<sup>4</sup> Infusion reaction should be coded in commercial EHRs to facilitate this change.

Second, we can combat cognitive bias by representing cutaneous findings from drug allergies in diverse patients. Such findings may present differently in patients of different ages, sexes, and races (see images). Clinicians should recognize that vancomycin infusion reaction may present with diffuse erythema, warmth without erythema, isolated palmar erythema, pruritus, urticaria, or in its severe form, symptoms indistinguishable from anaphylaxis. Availability of more diverse images of dermatologic findings can mitigate cognitive biases, such as prototype bias, which leads clinicians to estimate disease probability on the basis of the presentation's alignment with known prototypes.

Third, we can institute multidisciplinary training on best practices for drug-allergy documentation. EHR documentation of drug allergies has deficiencies that extend beyond vancomycin infusion reactions. Despite the importance of such documentation to the quality and safety of care, few clinicians receive training in

this area. The minimum useful information in a drug-allergy EHR entry is the drug and the reaction; additional details that could improve subsequent care include date, severity, clinical context, and treatment details. Since myriad health care professionals enter drug allergies in the EHR, training should occur across disciplines.

Fourth, including experts such as allergy specialists in our quality and safety infrastructure and on multidisciplinary antimicrobial stewardship teams can help improve antibiotic-allergy documentation, clarify drug-allergy diagnoses, and optimize antibiotic choices. Pharmacists, particularly those focused on antibiotic stewardship, also represent an invaluable resource for improving antibiotic-allergy documentation.

Finally, race-based reporting of clinical research examining racial differences needs to be challenged. Researchers should acknowledge that race is a social construct and explore how racism, rather than race, contributes to racial inequities.<sup>1</sup> It was not that Black patients had different biologic mast-cell responses to vancomycin, but rather that their vancomycin infusion reaction was not identified or not documented.

Implementing these recommendations would mean not only striking racist terminology from our professional vocabulary, but also improving the diagnosis and documentation of all allergic drug reactions for greater clinical precision and patient safety. It would move us one step closer to a safe, just, and equitable health care system.

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From the Divisions of Allergy and Clinical Immunology and of Clinical Pharmacology (S.A.A.) and the Department of Medicine (S.M.O.), Johns Hopkins University, and the Johns Hopkins Center for Health Equity



(S.M.O.) both in Baltimore; and the Department of Medicine, Brigham and Women's Hospital (T.D.S.), Harvard Medical School (T.D.S., K.G.B.), and the Division of Rheumatology, Allergy, and Immunology (C.M.B., K.G.B.), and the Edward P. Lawrence Center for Quality and Safety (K.G.B.), Massachusetts General Hospital all in Boston.

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## Beyond the Rubble of Lake Street Minds in Crisis in a City in Crisis

Rebecca Grossman-Kahn, M.D.

It is May 2020 in Minneapolis. Covid-19 reached us a few months ago, bringing daily routines to a halt. The few cars on the roads speed by, but the city is hushed. We are still wearing sweaters indoors, biding our time until summer heat arrives and until life returns to normal.

Then George Floyd is murdered on the street, and the city ruptures. Bursting out of their Covid cocoons, people unfurl their rage and flow into the streets. Summer heat arrives overnight. The threat of Covid fades in comparison to the weight of injustice.

The protests center on Lake Street, a commercial thoroughfare of South Minneapolis. Nearby, beyond the rubble of the burned storefronts, is the hospital where I'm training to be a psychiatrist. I treat people whose thoughts have become too jumbled, overwhelming, or terrifying for them to perform their daily tasks.

One morning, I meet a man whose wife brought him in the previous night. His hair is thick with grease and grime from Lake Street, where he's been protesting for a week since George Floyd's murder. He sits erect, his eyes scanning the room. I need to leave, he pleads. I have important work waiting for me out there.

As a psychiatry intern, I'd heard such entreaties before when initially meeting a patient. I have to get out of here because your computer is controlling my thoughts or Let me go before the underground fumes poison us all. But this plea sounds different.

I am needed out there in the fight for racial justice. I've been chosen as the leader. The man stands up and paces the exam room with electric energy. I've never been a political person, he continues, his words pulsing in time with his steps. I don't know much about activism, but when this started I drove downtown and watched the throng of people. I went home that night and the words on all those marching cardboard signs . . . they kept flashing in my mind. I tucked my son into bed and thought, What will be different for him?

I listen as he explains that our society needs treatment, not him. He doesn't pause between thoughts, so I have to interrupt to ask, What worried your wife enough to bring you to the hospital?

He replies, All I know is I'm showing up on Lake Street, and I'm needed there. He walks toward the door. What will change if we don't act today? This can't wait!

He's right. It can't wait. Why is

he at the hospital for raising his voice against injustice? My impulse is to thank him for his leadership and send him back to the protest. He denies being sick with the same fervency with which he calls on Minneapolis to face racism. I feel amazing, he says. I'm finally fighting for my children's future.

One devastating symptom of psychosis can be anosognosia, the lack of awareness of one's symptoms. I have been learning the heart-wrenching calculus of determining when someone's mental illness puts them or others at such high risk of harm that they should stay in the hospital, even when they disagree. Sometimes it's clear—a woman with a delusion that her partner is poisoning her attacks him in perceived self-defense; a man drives 160 miles an hour, unaware of potential consequences. But when changes are more subtle, making the decision involves long conversations with the person and the family. What will this man's wife say? I settle into a chair to learn more.

Things have been tough since Covid, she starts. He lost his job. He was drifting, without purpose. The protests were the first time he'd left the house in weeks. But then the protests became unpredictable. When the city curfew