



Disparities in the Diagnosis and Management of Anaphylaxis

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Accepted: 3 October 2022 / Published online: 1 December 2022

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Abstract

Purpose of Review The goal of this review is to characterize health disparities impacting the recognition and treatment of anaphylaxis.

Recent Findings Previous research has identified major health disparities related to atopic conditions including asthma, atopic dermatitis, and food allergies (FA); however, disparities related to anaphylaxis have yet to be examined in depth.

Summary We found widespread health disparities in the incidence and severity of anaphylaxis, as well as in the management of allergies (particularly food allergies) that place individuals at risk of anaphylaxis. Sociodemographic factors are associated with numerous negative health outcomes related to anaphylaxis. We highlight several key steps that must be taken to address these disparities.

Keywords Anaphylaxis · Allergy · Health disparities · Social determinants of health

Introduction

Anaphylaxis is a severe, systemic hypersensitivity reaction that is one of the most dangerous manifestations of allergic disease. Clinically, anaphylaxis is rapid in onset, and involves potentially life-threatening airway, breathing, and/or circulatory problems that are often, but not always, associated with skin and mucosal involvement [1]. Appropriate management of anaphylaxis centers around prompt treatment with intramuscular epinephrine, typically administered through an epinephrine autoinjector (EAI) [1]. While the mortality rate for anaphylaxis remains low in the USA, at less than 1 death per million annually over the past 20 years, anaphylaxis-associated anxiety, stress, and psychosocial burdens are substantial for patients and their families [2, 3].

Previous research has identified major health disparities related to atopic disorders including asthma, atopic dermatitis, and food allergies (FA) [4, 5]. However, disparities related to anaphylaxis have yet to be examined in depth. Given the severity of this condition, and the importance of early identification, education, and management in decreasing its potential negative impacts, it is important to understand the health disparities impacting the recognition and treatment of this condition. Since the incidence, type, and severity of allergies are central to understanding who is at risk of developing anaphylaxis, disparities related to food, medication, and insect allergies will also be briefly reviewed.

Epidemiology and Demographics of Anaphylaxis

Available data suggests that rates of anaphylaxis have increased in recent decades [6]. From 1990 to 2015, hospital admissions for anaphylaxis increased globally both for all-cause anaphylaxis and based on common triggers (foods, medications, and insect stings) [6]. Anaphylaxis accounted for 0.26% of overall hospital admissions in a recent multinational review, with differences noted by country [6]. In the USA, emergency department visits for anaphylaxis related to both FA and medications increased significantly among children ages 5–17 from 2005 to 2014 [7]. Hospitalization

This article is part of the Topical Collection on *Anaphylaxis and Drug Allergy*

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for food-induced anaphylaxis also more than doubled from 2000 to 2009 [8].

Race and ethnicity appear to be associated with both the incidence and severity of anaphylaxis. Black individuals have an increased risk of fatal food-induced anaphylaxis relative to White populations in the USA [9]. From 1999 to 2010, rates of fatal anaphylaxis increased in Black males in the USA, but were stable among Black females, White, and Hispanic populations over the same period [9]. Black and Hispanic children have higher rates of FA-related anaphylaxis, and are also more likely to present to the emergency department for anaphylaxis relative to White children [10, 11]. In the UK, South Asian children were over five times more likely to present with severe anaphylaxis (as defined by the Brown grading system) in comparison to their White peers [12].

Several potential factors could be contributing to these observed disparities. Asthma has also been identified as an independent risk factor for fatal anaphylaxis and, in one study, was present in more than two-thirds of cases of fatal anaphylaxis [1, 2]. During anaphylaxis in asthmatic patients, it has been theorized that increased bronchospasm and laryngeal edema may result in respiratory arrest/hypoxia that precipitates cardiovascular arrest more rapidly in this population [2]. Black populations are known to be at a significantly higher risk for asthma in comparison to other demographic groups, in part due to poor housing conditions rife with indoor triggers for asthma and increased exposure to air pollution, both of which are a legacy of widespread structural racism in housing policies [10, 13]. It has been speculated that increased asthma rates could underlie the increased frequency and severity of anaphylaxis in Black populations. However, whether a causal relationship exists between asthma and fatal anaphylaxis is unclear, in part due to the fact that individuals with FA (who are at increased risk for anaphylaxis) are far more likely to have a history of asthma than the general population [2].

Food Allergy and Anaphylaxis

The prevalence of food allergy in the USA is significantly higher in Black, Asian, and Pacific Islander children compared to White, non-Hispanic children [14, 15]. Black children are almost twice as likely as White children to report any probable food allergy (OR 1.8), and are more likely to exhibit food allergen sensitization and the development of multiple food allergies [14, 16]. An increased propensity for allergic diseases has also been recognized among Asian children in the USA, particularly after adjusting for the protective effects of foreign birth [17]. There is a particularly pronounced risk of atopic diseases in the Filipino population, with 57% higher odds of food allergy relative

to non-Asian children [17]. Indeed, while portrayals of FA in popular media tend to frame the condition as primarily impacting affluent, White communities, in reality, FA disproportionately affects many racial and ethnic minority populations, as well as those of lower socioeconomic status [4•]. It is estimated that while FA prevalence is increasing in the general population by about 1.2% per decade, among Black Americans, it is increasing at almost double this rate, at 2.1% per decade [18]. The reasons for these demographic trends are not yet known, but are believed to reflect a complex interplay of diet, environment, public awareness, and social determinants of health.

When food-allergic children have not been evaluated or diagnosed with allergy by a physician, their caregivers and families may remain unaware of the risk of anaphylaxis, as well as the importance of immediate intervention when signs of anaphylaxis appear. They are also unlikely to have access to a prescribed EAI or an emergency action plan, and are subsequently unable to share these resources with other caregivers, teachers, and family members who may be involved in the care of the child. Despite increased prevalence of FA, Black children have historically been significantly less likely than their White peers to have been diagnosed with FA by a physician [14]. In one study, Black children made up 27.0% of the population of undiagnosed FA (vs 20.4% of diagnosed FA), while White children comprised 39.2% of undiagnosed FA (vs 52.7% of diagnosed FA) [19]. A school-based study in New York City found that likelihood of providing physician documentation of FA was greatest among White students as well as those of higher socioeconomic status [20]. In another study, only 14.4% of Mexican American children with FA had received a physician's diagnosis, compared to 67.9% of White children [21]. Differences in access to care and disparities in the AI workforce are both thought to contribute to these differences [22, 23].

Even when FA has been documented by a physician, management and outcomes may remain suboptimal. In a study of food-allergic children at a clinic in New York serving an urban minority population, under 40% of children with a physician-diagnosed FA had a documented emergency action plan, less than half had their FA evaluation by an allergy specialist, and among those referred to an allergist, many either did not schedule an appointment or did not attend appointments that were scheduled [16]. When they do see an allergy specialist, Black and Hispanic children have a significantly shorter duration of follow-up than their White peers [10].

In a National Health Interview Survey (NHIS), families of Black children with FA were more likely to report food insecurity, difficulty paying medical bills, and difficulty affording prescriptions compared to White children with FA [23]. Families of Hispanic children with FA were more likely to report having difficulty paying for follow-up care. These

differences persisted even after adjusting for household income and parental education, reflecting the many social and economic barriers preventing families from accessing care even when a diagnosis or referral is provided, including out-of-pocket costs, obtaining time off work or school, and language/cultural barriers [23].

Further studies support an association between atopic disease management and socioeconomic factors. In a cross-sectional study using a patient-reported questionnaire in New York City schools, children from low-income households and those with public health insurance were the least likely groups to report undergoing recommended allergy testing as part of comprehensive asthma management (OR 0.18 and 0.46, respectively) [21]. Children with FA who were insured by Medicaid had significantly fewer follow-up appointments with allergists than those with private insurance [10]. Lower caregiver health literacy and food insecurity have also been linked to increased FA reactions, reflecting potential knowledge gaps in the understanding of FA, as well as decreased ability to provide safe foods to food-allergic children due to increased cost, food deserts, and other factors impacting food access [24, 25]. Significantly higher rates of anaphylaxis have also been identified in urban populations compared to rural populations [11]. In one study of anaphylaxis-related ED visits from 2009 to 2014, the increased rate of ED visits among Black children was largely driven by urban residence [11].

Drug Allergy and Anaphylaxis

Drugs have been identified as the most common cause of fatal anaphylaxis in adults [26]. Avoidance of drug-related anaphylaxis and other adverse drug events (ADE) requires accurate documentation in the medical record. Several studies have identified disparities in such drug allergy documentation, placing some patients at higher risk of adverse reactions. One study found that in comparison to White patients, Latino and Asian patients were significantly less likely to have appropriate documentation of drug allergy in the medical record [27]. Authors noted that these groups are more likely to report English as a second language, suggesting that language barriers may play a role in documentation errors [28]. Of note, similar disparities were not noted between Black patients relative to White patients in this study, where such language barriers did not occur.

However, another study found that Black patients were significantly less likely to have accurate documentation of vancomycin hypersensitivity reaction and penicillin allergy [29, 30]. Some of this disparity may relate to a decreased ability to recognize cutaneous reactions on darker skin tones, which itself may be a product of decreased representation of skin of color in medical textbooks and training [31]. One study found that medical students were significantly less

likely to recognize common dermatologic conditions in skin of color, including urticaria, which was correctly identified in only 57% of cases [32].

Race and ethnicity may also be associated with the risk of severe non-IgE-mediated drug reactions, potentially due to genetic factors [33••, 34]. Black African/Caribbean Americans were 3 to 4 times more likely than White patients to develop ACE inhibitor-induced angioedema in one study [35]. Another cohort study found that Black, Asian, and Pacific Islander patients had substantially higher risk of allopurinol-related ADE in comparison to White patients, with a particularly pronounced disparity among older women [36]. As previously noted, a significant association has been identified between risk of fatal anaphylaxis from drug allergy and African American race [9].

Insect Allergy and Anaphylaxis

Relatively little research has examined the impact of health disparities on the recognition and treatment of venom allergy. Insect stings and bites are a source of potentially fatal allergic reactions [37]. Fatal insect venom reactions tend to occur primarily in men, with 80–90% male predominance in some studies, which may reflect an interaction with pre-existing cardiovascular disease [26]. In the USA, White race is a risk factor for fatal venom anaphylaxis [26]. Other risk factors include older age, comorbidities (e.g., cardiovascular disease, asthma), medication use (beta blockers, ACE inhibitors), and mast cell disorders. The standard of care following severe reactions is venom immunotherapy. While studies on racial and ethnic differences in venom immunotherapy are not yet available, studies of allergy immunotherapy (AIT) for other indications show clear racial differences, with White patients significantly more likely to receive AIT than Black, Asian, or Hispanic patients [38, 39]. Further research is needed to determine the impact of health disparities in venom anaphylaxis and its management.

Epinephrine Access and Use

When anaphylaxis does occur, the immediate administration of epinephrine (and in some cases, multiple doses of epinephrine) is crucial to decrease morbidity and mortality. The fatality risk among children with FA increases by 10- to 100-fold if they lack access to an EAI [40]. Yet, numerous studies have identified widespread disparities in access to this life-saving medication. The retail purchase price of EAI varies widely based on location and insurance coverage, though often carries a substantial out-of-pocket cost (in 2016, estimated at up to \$690 per dual-pack package) [40]. EAI shortages are also an ongoing problem, with

direct effects on patient access [41]. Furthermore, devices typically expire within 18 months, requiring annual renewal [40]. Delayed administration of epinephrine is also associated with worse outcomes in anaphylaxis, reflecting the importance of appropriate education on anaphylaxis management, as well as access to, and appropriate use of, EAI for individuals with known allergies [2].

Given these substantial financial burdens, low-income populations are significantly less likely to have ready access to EAI. In a cross-sectional study of Medicaid patients treated for anaphylaxis in the pediatric emergency department, only 64% received a prescription for an EAI during their ED visit, 86% of whom went on to fill their prescriptions with Medicaid [42]. A population-based survey in Toronto in 2006 found that children from middle- and high-income homes were substantially more likely to report having a prescription for epinephrine (OR 8.35) [43].

Racial disparities also persist in this area. One multicenter study found that only 22% of patients presenting to the ED for anaphylaxis received discharge prescriptions for EAI, and White patients were 2.7 times more likely to receive an EAI prescription [44]. In another study, among patients discharged from the ED with EAI prescriptions, non-Hispanic White patients are more likely to fill their prescriptions when compared with non-Hispanic black patients [45]. Similarly, Medicaid patients were less likely to fill their EAI prescriptions than patients with private or Tricare insurance, though these differences were not statistically significant when accounting for multiple variables [45].

In a survey of parents of children with FA, White participants were significantly more likely to appropriately identify food allergy triggers and the symptoms of an allergic reaction than non-White participants, while Black and Hispanic parents were more likely to recognize the importance of food allergen avoidance in comparison to White parents [46]. Another study found that low health literacy of caregivers was associated with decreased knowledge on the appropriate management of allergic reactions, as well as decreased likelihood of demonstrating the correct use of an EAI [24]. These findings highlight the importance of clear, culturally competent education with parents regarding recognition and management of severe FA reactions.

Anaphylaxis in Schools

Disparities are also widespread with respect to anaphylaxis preparedness in schools. Schools are the most common public setting for anaphylaxis [47]. Even after controlling for the number of children with FA, schools serving high SES populations were almost 6 times more likely to report having EAI available relative to low SES schools [48]. Limited English proficiency was associated with decreased epinephrine

availability [48]. Schools in rural regions were also found to have decreased availability of EAI, and were the least likely to have protocols in place for staff to manage severe allergic reactions among students [49]. In a study of over 20,000 students enrolled in Massachusetts school districts from 2003 to 2004, 181 of whom were dispensed EAI for FA, White students were more almost five times more likely to have been dispensed epinephrine relative to non-White students, both for FA overall and peanut/tree nut allergy specifically (OR 4.76 and 4.5, respectively) [50]. In another study, while Black children were less likely to have a medication administration form (reflecting active involvement of a physician in their FA management), they were more likely to require epinephrine administration at school [20].

Hospitalization for Anaphylaxis

Data are conflicting with respect to hospitalization for anaphylaxis. Hospitalization rates related to food-induced anaphylaxis did not differ significantly by race or ethnicity in two studies [8, 51]. Similarly, in an analysis of New York State hospitalizations for food allergy among individuals under 20 years old from 1990 to 2006, no difference in hospitalization rate was observed between Black and White individuals [52]. In a study examining hospitalization for FA-related anaphylaxis, African American, Hispanic, and Native American patients in the lowest income quartile were disproportionately affected, as well as patients covered by Medicaid [53]. Another study examining trends from 2006 to 2015 found that the biggest predictors for hospitalization after presenting to ED for anaphylaxis were male sex, private insurance, higher household income, and presentation to an urban or metropolitan teaching hospital [54]. These discrepancies may be explained by some combination of socioeconomic factors as well as vastly different institutional policies regarding inpatient monitoring following anaphylaxis.

Limitations

There are still major limitations in our understanding of the role of health disparities in anaphylaxis. The true incidence of anaphylaxis is difficult to ascertain, given the challenges of measuring events in the community, outside of a medical setting [6]. The vast majority of studies on anaphylaxis do not examine outcomes in the context of social determinants of health. Even among those that do, there is substantial variability and lack of standardization in methods of diagnosing anaphylaxis [33••].

Table 1 Key anaphylaxis disparities

| Domain | Disparities noted |
|-------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Anaphylaxis incidence and severity | <ul style="list-style-type: none"> • Black individuals have an increased risk of fatal food-induced anaphylaxis [9] • Black and Hispanic children have higher rates of FA-related anaphylaxis [10] • Rates of fatal anaphylaxis increased in Black males from 1999 to 2010 [9] • South Asian children in the UK were over five times more likely to present with severe anaphylaxis than White children [12] |
| Food allergy (FA) | <ul style="list-style-type: none"> • Black children with FA are less likely to have been diagnosed with FA by a physician [14] • Mexican American children with FA received a physician's diagnosis at much lower rates than White children (14.4% vs 67.9%) [21] • Black children were less likely to have received an EAI prescription, an emergency action plan, and referral to an allergist [16] • Black and Hispanic children have a significantly shorter duration of follow-up with allergists their White peers [10] • Families of Black children with FA were more likely to report food insecurity, difficulty paying medical bills, and difficulty affording prescriptions compared to White children with FA [23] • Families of Hispanic children with FA were more likely to report having difficulty paying for follow-up care [23] • Children with FA insured by Medicaid had significantly fewer follow-up appointments with allergists than those with private insurance [10] |
| Drug allergy | <ul style="list-style-type: none"> • Latino and Asian patients are significantly less likely than White patients to have appropriate documentation of drug allergy in the medical record [27] • Black patients were significantly less likely than White patients to have accurate documentation of vancomycin hypersensitivity reaction and penicillin allergy [29, 30] • Black African/Caribbean Americans were 3–4× more likely than White patients to develop ACE inhibitor-induced angioedema [35] • Black, Asian, and Pacific Islander patients had substantially higher risk of allopurinol-related ADE in comparison to White patients [36] |
| Epinephrine access and use | <ul style="list-style-type: none"> • Canadian children from middle- and high-income homes were substantially more likely to report having a prescription for EAI [43] • White patients were 2.7 times more likely to receive an EAI prescription compared to Black patients [44] • Black patients were significantly less likely to fill their EAI prescriptions compared with White patients [45] |
| Anaphylaxis in schools | <ul style="list-style-type: none"> • Schools serving high SES populations were almost 6× more likely to report having EAI available relative to low SES schools [48] • Limited English proficiency in the student body is associated with decreased epinephrine availability [48] • White students were more almost 5× more likely to have been received epinephrine in school relative to non-White students [50] • Black children were less likely to have a medication administration form for EAI, but more likely to require epinephrine administration at school in comparison to White children [20] |

Conclusions

Health disparities are ubiquitous in the USA, and disparities in the recognition and management of anaphylaxis are no exception (Table 1). Race and ethnicity are associated with numerous negative health outcomes related to anaphylaxis. While genetic traits have been associated with risk of drug allergy, in the vast majority of cases, it is the effect of racism and systemic bias, not genetic or biological factors, that underlies these differences. Structural and systemic racism have contributed to increased rates of poverty, decreased access to health care, harmful environmental exposures, chronic and toxic stress, and lower health care quality for many racial and ethnic minority groups, all of which can contribute to the disparities surrounding anaphylaxis [33••].

There are many critical steps that must be taken to address these disparities. A recent AAAAI working group on addressing health disparities in Allergy/Immunology (A/I) laid out several important interventions to address disparities in allergic conditions overall, including addressing social determinants of health, improving community partnerships, increasing access to subspecialty care, and increasing training to reduce implicit bias in health care [33••]. Given the lack of research in many aspects of A/I health disparities, increasing inclusivity in clinical studies (particularly for diverse and vulnerable patients) should be a priority in future research [55]. It is also essential to increase diversity in the A/I workforce to ensure it is reflective of the patient populations it serves [22, 55]. Sociodemographic, economic, and environmental obstacles can have profound

negative effects in the recognition and management of anaphylaxis. Addressing these disparities is of the utmost importance for the field of A/I.

Compliance with Ethical Standards

Conflict of Interest Julie Wang declares research support from the National Institute of Allergy and Infectious Diseases, Aimmune, DBV Technologies, and Regeneron, and consultancy fees from ALK Abello and Jubilant HollisterStier. Brit Trogen and Samantha Jacobs declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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