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Contribution of antimicrobials to the development of allergic disease

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Antimicrobials represent a broad class of chemicals with the intended purpose of eliminating or controlling the growth of harmful microorganisms. Exposure can occur occupationally or through the use or consumption of consumer products. The use of antimicrobial agents has been associated with an increased incidence of allergic diseases, including asthma, atopic dermatitis, and less commonly, anaphylaxis. Very diverse immunological mechanisms and mediators have been identified in the sensitization response to antimicrobial chemicals and the importance of the local microenviroment in the response is increasingly being recognized. A complete understanding of the mechanisms of allergic diseases resulting from antimicrobial exposure will help to ensure safe environments and exposure limits.

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Introduction

Antimicrobials represent a broad class of chemicals that include sterilizers, disinfectants, sanitizers, and preservatives with the intended purpose of eliminating or controlling the growth of harmful microorganisms such as bacteria, fungi, and viruses. The range of specificity and the effectiveness of antimicrobial agents are very diverse based on the type/types of chemical(s) used. While the importance of these antimicrobial chemicals is understood, exposure to many of these agents is known to directly induce a variety of health effects including allergic disease [1,2].

Allergic disease can be influenced by several factors elicited by the exposure itself (i.e. source, exposure route, the environment) and by factors inherent to the exposed individual (i.e. genetics, immune status, personal habits). Allergic diseases are characterized by a latency period between primary exposure (sensitization) and symptoms (elicitation) that develop upon subsequent exposures, and may involve IgE and/or non IgE-mediated responses. An IgE-mediated allergic reaction (sometimes called immediate-type hypersensitivity (Type I)) involves the production of Th2 cytokines, such as IL-4 and IL-13, which initiate IgE production by B cells; the elicitation phase (symptoms) is caused by IgE-driven mast cell degranulation. These reactions may occur in various organs resulting in diseases such as asthma, allergic rhinitis, urticaria, and anaphylaxis. A non-IgE-mediated or delayed-type hypersensitivity response (Type IV) is T cell-mediated and elicitation is characterized by excessive inflammation, initiated by responding memory T-cells. The most distinctive feature of a non-IgE-mediated hypersensitivity response is the delay observed between allergen exposure and the elicitation immune response. Following sensitization, subsequent exposures result in secretion of pro-inflammatory cytokines that activate and recruit macrophages and other immune cells. Allergic contact dermatitis (ACD) is an example of a non-IgE-mediated hypersensitivity reaction. Interestingly antimicrobials are low molecular weight chemicals that can induce divergent immune mechanisms and can result in multiple types of allergic disease including those described above. This review will focus on the description of specific antimicrobials that have been associated with sensitization along with research advancements that have helped us to better understand the mechanisms of disease.

Occupational and consumer exposure to antimicrobial chemicals

Workers in health-care and clinical facilities have one of the highest incidences of allergic disease compared to other industrial sectors [3,4]. Individuals in these settings are frequently exposed to a variety of high-level cleaners and disinfectants (alcohol, chlorine, iodine-based agents, phenols, hydrogen peroxide, and quaternary ammonium compounds (QACs)) along with antiseptics for the purposes of sterilization of surfaces and medical/surgical instruments, and reducing the incidence of nosocomial infections. It has been estimated that asthma among health care workers accounts for about 16% of all occupational asthma cases [5] and that up to 24% of these cases are due to exposure to cleaning agents [6], including formaldehyde, glutaraldehyde, hypochlorite bleach,

hydrogen peroxide, and enzymatic cleaners [1,7]. Additionally, nurses have been identified to have a higher risk of asthma compared to administrative staff, and tasks with the highest incidence of asthma include those resulting from dilution of disinfection products by manual mixing [8]. In general, there are also increased rates for ACD for health care workers compared to non-health care workers [4] due to exposure to numerous antimicrobial agents including formaldehyde and biocides [9,10]. Although most common in health care workers, there is also an increased incidence for allergic disease in janitors/cleaners, hairdressers, dental assistants, veterinarians, food preparation/service workers, and metalworkers as a result of antimicrobial exposures [9].

Some of the most common allergens in the health care profession include biocides and disinfectants commonly used for the sterilization of medical devices which are sensitive to normal heat or steam sterilization and the disinfection of surfaces [11]. Exposure to the high-level disinfectants, glutaraldehyde and OPA, has been associated with dermatitis and occupational asthma [12–15]. QACs (sprays and wet-wipe products used for disinfecting surfaces and floors) are also common occupational allergens and have been associated with both contact dermatitis and occupational asthma [8,11,16–19]. Additionally, clinical antibacterial hand sanitizers and soaps containing chemicals including chloroxylenol, triclosan, and cocamide diethanolamine have also been associated with allergic disease [11,20,21]. Chlorhexidine gluconate is commonly used as an antiseptic applied directly to the skin to prepare for surgery. Although rare, serious allergic reactions including anaphylaxis have been reported following exposure [22].

In addition to occupational exposures to antimicrobial chemicals, there is also concern for exposures to the general population via consumer and food products including: cleaners and disinfectants for non-critical surfaces, algaecides, fabric softeners, cosmetics, moisturizers, antistatic agents, and food additives and preservatives. The use of antiseptics, disinfectants, detergents, and preservatives has also increased their incorporation into consumer products that are utilized orally (toothpaste and mouthwash) or applied to the skin or eyes (nasal sprays, makeup, lotions, and ophthalmic drops) for the purpose of decreasing microbial contamination and reducing the incidence of pathogen-induced illness. In general, antimicrobials exhibit a wide spectrum of activity; and new ones are constantly being developed/modified for specific purposes.

Novel mediators involved in sensitization to antimicrobial agents

As mentioned earlier, exposure to antimicrobial chemicals can result in multiple hypersensitivity pathways/disease outcomes (i.e. both type I/type IV; ACD and asthma), which increases the complexity of the immunological mechanism driving the response. Further research is needed to evaluate the hazard-potential and to fully understand the immunological mechanisms that induce and exacerbate allergic diseases. Recently, our laboratory found that a QAC, didecyldimethyl ammonium chloride (DDAC), is a strong dermal sensitizer [16]. Although DDAC displays many of the immunological attributes of a T-cell mediated sensitizer, dermal exposure also results in increased production of IgE and Th1 and Th2 cytokines, indicating a mixed-type allergic response [23]. Further investigation into these responses showed that DDAC induced high levels of expression of the Th2-skewing cytokine TSLP, which has been shown to activate Type 2 Innate Lymphoid cells (ILC2s) in the skin. ILC2s, a subset of innate lymphocytes that lack rearranged antigen-specific receptors and produce Type 2 cytokines, have recently emerged as mediators of allergic disease [24]. Following DDAC exposure, ILC2s in the skin were rapidly activated, and their activation coincided with the production of type 2 cytokines in the absence of T cells, providing a potential mechanism for the initiation of the mixed-type allergic response.

As exemplified by the study described above, it is becoming increasingly recognized that sensitization can be influenced by the local microenvironment. Recently, mitochondrial dysfunction has been shown to influence multiple hypersensitivity pathways [25], and antimicrobial chemicals have been demonstrated to negatively affect mitochondrial function in cells present at sites of antimicrobial exposure [26,27]. Triclosan has been identified as a mitochondrial uncoupler (decreases ATP and increases oxygen consumption rate) of mast cells, human primary keratinocytes, and *in vivo* in live zebrafish at non-cytotoxic concentrations [28,29]. Additional mitochondrial effects including altered morphology, calcium levels, and membrane potential were also observed following exposure [30]. Similarly, QAC exposure induced mitochondrial fragmentation and shifts in mitochondrial bioenergetics in epithelial cells [26]. Many of these mitochondrial alterations, including morphology and bioenergetics dysfunction, can elicit proinflammatory upregulation which could influence hypersensitivity response [29]. Understanding how novel mediators (which are often tissue-specific) initiate the development of allergic immune responses at the site of antigen contact will be crucial to predicting the allergic nature of antimicrobials and understanding the type of disease that may manifest due to exposure [31].

Antimicrobials and increased allergic susceptibility

While certain antimicrobials, including those described above, are known to induce sensitization, others such as triclosan have been associated with allergic disease, although not directly sensitizing. In addition to its clinical

use, triclosan is used as a preservative, fungicide, and biocide in household and personal care products [29,32,33]. Research suggests that triclosan exposure may be at least in part responsible for recent increases in the frequency of asthma and allergic disease [20,34,35]. Additional studies have revealed that topical exposure to triclosan augmented the allergic response to an experimental allergen through a thymic stromal lymphopoietin (TSLP)-mediated pathway in a mouse model of asthma [34,36]. The increased Th2 response would likely result in a decreased Th1 response, which could potentially increase an individual's susceptibility to infection and/or disease [37]. Triclosan has been also shown to have direct effects on skin cells [38], which can influence the local microenvironment and immune response [39]. More specifically triclosan has been identified to induce abundant expression of S100A8/A9 in the skin, which acts as an endogenous ligand for the intracellular signaling receptor TLR4, which is responsible for activation of the innate immune system [30]. Similar to triclosan, parabens are preservatives found in a wide range of products encountered daily. Parabens were identified to be useful antibacterial and antifungal agents leading to their use as a preservative. The odorless, colorless, and inexpensive qualities made them a primary choice when trying to extend the shelf life of cosmetics, pharmaceuticals, and other consumer goods. In a review of cosmetic ingredients, 87%–93% of cosmetic products contained at least one paraben [9]. Despite frequent use, the incidence of allergy to parabens is relatively low [4]. Interestingly, disruption of the epidermis including compromised or inflamed skin, which can result from genetic predisposition, is often a prerequisite for ACD resulting from paraben exposure [40,41]. While research does suggest an association between paraben exposure and asthma, existing literature is conflicting [42–44]. Confounding factors include: prenatal versus postnatal exposures; prevalence versus morbidity outcomes, and sex-differences. Additional investigations are warranted.

Antimicrobials and the microbiome

As most antimicrobials used in both the workplace and commercial products are broad spectrum, the potential exists that antimicrobials applied in products may influence an individual's microbiome. The importance of the microbiome in immune responses is increasingly being recognized, including the development of allergic disease. 16S rRNA sequencing results revealed that 13-week triclosan exposure in drinking water induced significant perturbations in mouse gut bacterial assemblages with distinct trajectories compared to controls [45]. Metagenomics sequencing results indicated a remarkable enrichment of gut bacterial genes related to triclosan resistance, stress response, antibiotic resistance, and heavy metal resistance. However, much less research has been conducted on the effects of antimicrobials on the skin microbiome. Many chemical sensitizers are also antimicrobial agents [12,16,18] and while these agents may be beneficial in protecting against pathogenic bacteria, the influence of exposure on resident bacterial populations warrants further investigations. Recently, skin commensals have been shown to play an important role in Th1 and Th2 balance along with the regulation of anti-inflammatory responses to chemical allergens [46]. Research has also shown that germ-free mice have elevated levels of TSLP, which suggests a role for the microbiota in ameliorating stress signals released by keratinocytes which could potentially influence subsequent immune responses [47]. Additionally, a recent study found that germ-free mice contain largely undifferentiated mast cells and reveal that the skin microbiota plays a significant role in the recruitment and maturation of dermal immune mast cells [48]. SanMiguel *et al.* found that topical treatment with antibiotics led to significant and stable changes in commensal bacterial populations in mice; however, antiseptics only resulted in short-term perturbations [49]. A follow-up study confirmed the rapid, but short-term effect on microbial communities in humans, and also showed that the depleting effect of antiseptics (80% ethanol and povidone-iodine) was dependent on body site and the composition of the microbial community with more dominant taxa being more resistant [50]. Another study showed that the antimicrobial preservative and QAC benzalkonium chloride (BAC) significantly reduced the microbiome (assessed by positive cultures) of the nasal cavity when delivered as a topical ocular lubricant [51]. BAC is present in more than 70% of ophthalmic drugs, highlighting the ubiquitous use of antimicrobials/preservatives in products used by consumers, and their potential impact on allergic disease [52].

Conclusions

While the use of antimicrobials is important for preventing infections, especially in clinical settings, there is also a responsibility to provide a safe and healthy environment for workers, patients, and consumers. The impact of antimicrobial agents is due not only to their sensitizing potency but also to their broad source of exposure and widespread use in daily life. While research demonstrates a role for antimicrobial chemicals in allergic disease, the exact mechanism of action for sensitization for most of these compounds remains to be investigated and explained. In addition, new chemicals are constantly being synthesized for specific antimicrobial purposes or as potentially fewer toxic alternatives and these may also present unique burdens on the immune system. A complete understanding of the mechanisms of allergic diseases resulting from antimicrobial exposure will allow for surveillance, proper treatment and/or prevention, while hazard identification will lead to risk assessment, which will ensure safe environments and exposure limits.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

Conflict of interest statement

Nothing declared.

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Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest

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