

Microbial Exposure and Asthma

Applying Strachan's Hygiene Hypothesis to Nursing Practice

Elisabeth Campbell

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Sharon Kopsis, Ed.D.
Chairman of Thesis

Cynthia Goodrich Ed.D.
Committee Member

Randy Hubbard, Ph.D.
Committee Member

James Nutter, D.A.
Honors Program Director

Date

Abstract

The incidence of asthma has risen significantly in recent decades. Asthma is a complex disease process affected by multiple factors including environmental exposure, genetics, epigenetics, and lifestyle. In 1989, the hygiene hypothesis was proposed based on Strachan's findings suggesting increased exposure to microbes may have protective benefits against allergic rhinitis and eczema. Since that time, research in this arena has exploded as investigators seek to establish a causal link between increased microbial exposure and decreased incidence of allergic disease. The aim of this literature review is to synthesize the current research regarding Strachan's hygiene hypothesis and identify the nursing implications of this theory, particularly in regards to patient care and education of pediatric clients and their families.

Microbial Exposure and Asthma:

Applying Strachan's Hygiene Hypothesis to Nursing Practice

The prevalence of asthma and allergies has increased in recent decades (Adler, 2005) around the world but particularly in western nations as well as some impoverished countries (Brooks, Pearce, & Douwes, 2013; Romagnani, 2004). Data from the National Asthma Control Program, headed by the Centers for Disease Prevention and Control (CDC), indicates that asthma is a prevalent problem in the United States, affecting one in eleven children and one in twelve adults in 2010. According to this national report, the proportion of individuals in the United States with asthma grew by 15% in the last decade, and the national cost of treating this illness is 56 billion dollars annually. Asthma can be debilitating and even lethal if patients do not receive appropriate treatment and management of their disease. According to the data from the CDC National Asthma Control Program, three in five persons with asthma in the United States are forced to limit their activity due to their diagnosis. According to this CDC report, nine individuals die each day from asthma, and in 2009 fatalities from asthma equaled 3,388 deaths (Centers for Disease Control and Prevention, n.d.). For this reason, understanding the pathophysiology of atopic diseases, such as allergies and asthma, has become a priority in order to treat and prevent atopic disorders (Bloomfield, Stanwell-Smith, Crevel, & Pickup, 2006).

To date, asthma causation is considered to be multifactorial (Prokopakis et al., 2013). Genetic predisposition, genetic expression, timing and types of environmental exposures have all been found to play a role in allergic disease and asthma development

(Prokopakis et al., 2013). Since these factors work together to cause the development of atopic diseases, studying any one factor individually may prove difficult. Exposure to microbial organisms, nevertheless, has received extensive research related to its role in allergy and asthma development (Brooks, Pearce, & Douwes, 2013; von Mutius, 2007).

Strachan's Hypothesis

A longitudinal study conducted by Strachan is considered the foundational study in research related to the relationship between infection and atopic disease. In Strachan's landmark study, he selected 17,414 British children born during one week in March 1958 and used interviews concerning babies' eczema during their first year of life and hay fever during the last 12 months at age 11 and age 23. Parental reports were used when the children were 1 year old and 11 years old, and self-reports were used when the study participants were 23 years old. Strachan used statistical analysis of variables and incidence of hay fever to determine associations. His analysis found that family size and the age order of the child seemed to have a significant impact on development of hay fever. Strachan found as family size and number of older children in a household increased, the incidence of hay fever declined. For this reason, he theorized that larger family sizes and a greater number of older children in the household contribute to greater exposure to microorganisms, and greater microbial exposure provides protection against hay fever development. Based on his findings, Strachan suggested that reduced exposure to infection due to hygienic practices has increased the prevalence of atopy in developed countries (Strachan, 1989).

Strachan's theory is now known as the hygiene hypothesis (Brooks, Pearce, & Douwes, 2013; von Mutius, 2007). Due to its potential ramifications for allergy and asthma treatment and prevention, the hygiene hypothesis has received considerable research in recent years (Bloomfield, Stanwell-Smith, Crevel, & Pickup, 2006; Brooks, Pearce, & Douwes, 2013). Although the hygiene hypothesis is still a matter of debate, microbial exposures have been credited with protective benefits related to the inverse correlation between diverse microbial exposure and atopic disease (Brooks, Pearce, & Douwes, 2013). While research of the hygiene hypothesis and the etiology of atopic diseases has been abundant (Bloomfield, Stanwell-Smith, Crevel, & Pickup, 2006), little has addressed nursing implications of this theory, particularly in regards to patient care and education of pediatric asthmatic clients.

Asthma and the Hygiene Hypothesis

Much research has been dedicated to studying the relationship between infectious exposure and the development of allergies and asthma. According to Brooks, Pearce, & Douwes (2013), protective effects have been attributed to array of infection types, including bacterial, viral, and parasitic. While various species of these microorganisms have been studied for their protective benefits or harmful effects on asthma development, it still remains unclear what is the most important factor for protection, specifically route of transmission, severity of infection, or location of the infection within the body. Since results for certain microbes have been inconsistent, some have suggested that protection against atopic disease is dependent upon the diversity of microbial exposure not just the type of infectious organisms (Brooks, Pearce, & Douwes, 2013).

Diversity of Microbial Exposure

Recent studies conducted by Ege et al. published in 2011 by *The New England Journal of Medicine* highlight the protective role of microbial diversity by relating the prevalence of childhood asthma and atopy with environmental exposures. The Prevention of Allergy—Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Lifestyle (PARSIFAL) and the Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community (GABRIEL) Advanced Study are two recent studies that have shown this correlation. Both the PARSIFAL and the GABRIELA studies measured microbial exposure and compared levels of exposure to presence of asthma in school-aged children. Both studies used written surveys which evaluated the extent of exposure to farming as well as allergic and respiratory symptoms (Ege et al., 2011).

In the PARSIFAL study conducted by Ege et al. (2011), dust was collected from children's mattresses using a vacuum cleaner and examined using single-strand conformation polymorphism (SSCP) analysis to determine the presence of bacterial deoxyribonucleic acid (DNA) which would otherwise be undetectable with cultures. In the GABRIELA study, dust samples were collected using electrostatic cloths mounted on plastic sample holders. The electrostatic dust collectors were placed in the children's rooms, where they remained for 14 days. The dust samples were cultured using five different culture mediums as well as examined for gram stain. Colonies on the culture mediums were counted after seven days of growth, and results were expressed based on

number of bacterial and fungal colony-forming units on each dust collector (Ege et al., 2011).

Results from both studies by Ege et al. (2011) showed that children living on farms were exposed to a greater diversity of microorganisms and were also less likely to have asthma. When results from both studies were analyzed, there was greater diversity of bacteria and fungi found in the rooms of children on farms as compared to their non-farming counterparts. There was also found to be a lower incidence of asthma in children with greater diversity of environmental exposures even if the child was not living on a farm. A decrease in atopy was, on the other hand, only weakly associated with increased diversity of microbial exposure. These findings support the idea suggested by the hygiene hypothesis that increased microbial exposure may have a protective effect against the formation of certain atopic diseases, in this case asthma (Ege et al., 2011).

Noninfectious Exposures

While there are protective benefits of diverse microbial exposure as noted above (Ege et al., 2011), the type of bacterial exposure can influence asthma development. According to Brooks, Pearce, and Douwes (2013), exposure to noninfectious Gram-positive and Gram-negative bacteria also confer protective benefits against asthma development. Thus, bacterial pathogens are not the only means of protection against atopy; interestingly, studies have also indicated a significant negative correlation between levels of bacterial endotoxins inside the home and atopic asthma. The effects of endotoxins are, however, not consistent since endotoxins in the urban inner cities are considered a risk factor for asthma development (Brooks, Pearce, & Douwes, 2013).

Challenges of the Hygiene Hypothesis

While the hygiene hypothesis has garnered support from research conducted around the world, according to Brooks, Pearce, and Douwes (2013), several challenges remain related to the seeming inconsistencies between epidemiological findings and the trends which were expected based on this hypothesis. For example, the prevalence of asthma is on the decline in certain western nations despite a lack of evidence for a correlating decrease in cleanliness or increase in family size. Despite the decline in asthma in western countries, there has not been a correlating decrease in other atopic diseases; instead, the prevalence of food allergies and atopic eczema continue to rise. In spite of the overall decline in asthma in the West, asthma is on the rise in urban inner cities, particularly among impoverished African-Americans, despite the fact that an increase in hygienic practices in this population is an unlikely explanation of this phenomenon (Brooks, Pearce, & Douwes, 2013).

Another problem with the hygiene hypothesis, as it was originally defined, is that it offers only a narrow explanation of asthma causation that does not fully account for the complexities of immunological development (Brooks, Pearce, & Douwes, 2013). It was originally thought that the protective benefits of microbial exposure against atopy were directly related to early exposure to microorganisms; however, recent evidence supports the idea that early as well as ongoing exposure to microbes are necessary in order to attain and maintain protection from asthma (Brooks, Pearce, & Douwes, 2013).

Clearly, a broader understanding of the hygiene hypothesis is needed in order to explain the etiology of asthma and other atopic diseases in the pediatric population. The

key to applying the current understanding of the hygiene hypothesis is to realize that this hypothesis accounts for only part of the underlying mechanism of atopic asthma. Further research is necessary in order to discover other underlying mechanisms, which will hopefully allow for better development of evidence-based treatment protocols (Brooks, Pearce, & Douwes, 2013).

Immune System Interactions

Asthma Pathophysiology

In recent decades there has been a significant increase in the incidence of atopic diseases, such as allergic rhinitis and asthma, in Western nations (Heederik & von Mutius, 2012). For this reason it is important to understand the pathologic mechanisms which underlie their development. In Strachan's study, he focused on two types of atopic disease, eczema and hay fever (Strachan, 1989), which is also known as allergic rhinitis (Hay fever, 2010). Recent studies have not been as limited in scope, but rather have included several types of hypersensitivities, including allergic rhinitis, asthma, and atopic dermatitis. In order to apply the vast amount of research on the hygiene hypothesis to nursing practice, it was necessary to limit the scope of this paper to asthma, which is one of the major diseases affecting children in the United States as reported in *Asthma's Impact on the Nation* by the CDC (Centers for Disease Control and Prevention, n.d.). According to the same report by the CDC, there were seven million children in the United States with asthma in 2010, and in 2009 one in five children in the United States visited the Emergency Department in order to receive asthma-related care (Centers for Disease Control and Prevention, n.d.).

Understanding how diverse microbial exposures could be potentially protective against the acquisition of asthma in childhood, thus, necessitates a discussion of the Type I Hypersensitivity reaction that occurs in atopic asthma pathophysiology (Huether & McCance, 2008). Atopic asthma is characterized by narrowing of the bronchial airways caused by an inflammatory response to allergens, which function as antigens that stimulate the release of inflammatory chemicals (Huether & McCance, 2008). When an asthmatic individual is exposed to an allergen, such as house dust mites, animal dander, pollen, or cigarette smoke, it triggers an immune response initiated by the epithelial and dendritic cells in the airways (Harper & Zeki, 2014). After processing environmental allergens, dendritic cells present these antigens to T cells, leading to clonal expansion of T helper2-type (Th2-type) lymphocytes and subsequent switching of B cells to produce Immunoglobulin (Ig) E (Harper & Zeki, 2014). These mature B cells, known as plasma cells, release IgE. Immunoglobulin E is rapidly bound to IgE-specific Fc receptors on the surface of mast cells, leading to sensitization of the individual to a particular antigen. Degranulation of mast cells leads to the release of histamine, a vasoactive amine that acts at histamine H1 receptors to increase vascular permeability and constrict smooth muscle in the bronchioles. Chemotactic factors, which are also released during mast cell degranulation, attract neutrophils, eosinophils, and lymphocytes to the airways, leading to a heightened inflammatory response (Huether & McCance, 2008).

Airway smooth muscle (ASM) cells are also thought to play a role in the airway hyperactivity characteristic of asthma since these cells have been shown to respond abnormally to allergens and have the ability to secrete inflammatory cytokines that recruit

mast cells to the site of inflammation (Harper & Zeki, 2014). These findings are significant since ASM, which surrounds the bronchi, contract and relax to control airway diameter and bronchomotor tone (Harper & Zeki, 2014). Bronchial constriction and increased vascular permeability caused by the inflammatory process leads to the classic signs and symptoms of an asthma attack, including airway edema, decreased air exchange, dyspnea, and wheezing (Huether & McCance, 2008).

Recently, the role of Toll-like receptors (TLRs) in the inflammatory response has been considered to be a part of the pathophysiology of asthma (Chen et al., 2011). Toll-like receptors belong to a group of innate receptors called pattern recognition receptors (PRRs) (Huether & McCance, 2008). These PRRs allow phagocytic immune cells to recognize patterns of cell-surface molecules, such as lipopolysaccharides (LPS), peptidoglycans, and lipoproteins, which are found on bacteria (Huether & McCance, 2008). For example, endotoxins, LPS molecules found on the cell walls of gram negative bacteria, are potent stimulators of TLR4 (Kindt, Goldsby, & Osborne, 2007). Toll-like receptors allow the phagocytes to bind to the pathogen, such as a bacterium, or its products, enabling them to be engulfed (Huether & McCance, 2008). There are currently eleven TLRs that have been identified in humans (Prokopakis et al., 2013). Toll-like receptors have been found on mast cells, neutrophils, macrophages, and epithelial cells (Huether & McCance, 2008), and knowledge of their functions is still expanding with increasing research (Prokopakis et al., 2013).

According to Chen et al. (2011), activation of the TLRs on the surface of immune cells can have several outcomes, including the differentiation of T helper (Th) cells,

specifically Th1, Th 2, and Th 17; activation of antigen presenting cells (APCs) and eosinophils; and mast cell synthesis of cytokines. When dendritic cells (DCs), a specific class of APCs, are activated during an allergic response, TLR engagement on the cell surface of DCs leads to the differentiation of Th cells into Th 2 cells, a cell type which is associated with allergic disease (Chen et al., 2011) and the activation of B cells, which produce antibodies such as IgE in the allergic response (Harper & Zeki, 2014). On the other hand, when an infant or child is exposed to a true pathogen, versus an allergen, the immune system is forced to mature, resulting in the differentiation of Th cells into Th 1 cells, deviating away from the proallergic Th 2 phenotype of Th cells (Chen et al., 2011). Instead of initiating the antibody response as Th 2 lymphocytes do, Th 1 cells activate cell-mediated immunity and recruit neutrophils, natural killer cells, cytotoxic T lymphocytes, monocytes and macrophages (Harper & Zeki, 2014). Based on the framework of the hygiene hypothesis, microbial exposure early in life stimulates TLRs and forces Th cell differentiation away from the Th 2 phenotype, which predominates *in utero*, toward the Th 1 phenotype, thereby, protecting individuals from allergic disease (Prokopakis et al., 2013). Deviation toward a Th1 instead of Th 2 type phenotype has, therefore, been hypothesized to generate the protective benefit of exposure to a diverse array of microorganisms in childhood and may, in effect, explain the immunological mechanism underlying the hygiene hypothesis (Chen et al., 2011).

Proposed Mechanisms of the Hygiene Hypothesis

As described above, Th cell differentiation can either promote or protect against allergy and asthma development (Brooks, Pearce, & Douwes, 2013; Chen et al., 2011;

Prokopakis et al., 2013). When Th cells differentiate into Th 1 cells, Th 1 cells produce cytokines, interleukin (IL) 2 (IL-2) and interferon (IFN) gamma (IFN-g), that inhibit Th 2 cell differentiation (Harper & Zeki, 2014). Conversely, when Th cells differentiate into Th 2 lymphocytes, Th 2 cells produce cytokines, such as IL-4, IL-5, and IL-13, which inhibit Th 1 cell differentiation (Harper & Zeki, 2014). While differentiation of Th cells away from the proallergic Th 2 phenotype toward the Th 1 phenotype is considered to be part of the underlying protective mechanism of the hygiene hypothesis (Prokopakis et al., 2013), it cannot fully explain the complexities of the immune response seen in numerous observational studies (Brooks, Pearce, & Douwes, 2013). For example, parasitic infections have been demonstrated to confer protective effects against atopy, yet they are associated with powerful Th 2 cell responses (Brooks, Pearce, & Douwes, 2013) and the production of IgE by B cells specific to parasitic antigens (Kindt, Goldsby, & Osborne, 2007).

The level of exposure to bacterial cell components, such as endotoxins, may also play a role in Th1/Th2 balance (Brooks, Pearce, & Douwes, 2013). Endotoxins are a type of lipopolysaccharide that comprises a portion of Gram-negative bacteria cell walls (Prokopakis et al., 2013). These LPS molecules may play a role in the pathophysiology of the hygiene hypothesis since increasing levels of endotoxins in household dust was associated with a decreased risk of future development of allergic rhinitis and asthma (Prokopakis et al., 2013). Interestingly, house dust in kitchens and children mattresses in rural homes had higher levels of endotoxins than non-rural dwellings, which may confer protective benefits for atopy (Prokopakis et al., 2013). Other studies have shown that

farm living is more closely correlated with protection against allergic diseases than simply living in a rural setting (Prokopakis et al., 2013). This is specifically related to the type of farming and exposure to farm animals and particular types of feed (Ege et al., 2007).

While bacterial exposure in the airways can protect against allergy-associated inflammation (Brooks, Pearce, & Douwes, 2013), exposure to Gram-positive and negative bacterial antigens in already sensitized individuals can promote rather than protect against inflammation, thereby, worsening already existing allergic diseases and asthma (Prokopakis et al., 2013). In the same way, exposure to viral illnesses can lead to asthma exacerbation and potentiate airway inflammation, increasing the symptoms of asthma (Kloepfer & Gern, 2010).

Epigenetics

Epigenetics, as defined by Prokopakis et al. (2013), is the study of heritable changes that are above the genome and affect gene expression yet do not change the actual DNA sequences within cells. These changes are mediated through DNA methylation and modification of histones and affect gene expression rather than the actual nucleotide sequences within DNA strands. These changes can last the entire life of the cell and may even be transmitted from one cellular family to the other by means of cellular division. This rapidly expanding field has received increased attention in recent years and may explain some of the role environmental factors, such as diet and the normal flora of the human gut, have on the development and balance of the immune system. While further research is needed to elucidate the relationship of epigenetics to the

hygiene hypothesis, it is possible that these non-genetic changes may partially explain the differences found among monozygotic twins, incomplete penetrance, and effects of gender and transference of parental traits on the development of allergic diseases (Prokopakis et al., 2013).

One specific environmental factor that has been identified to play a role in epigenetics and the hygiene hypothesis is diet (Prokopakis et al., 2013). For example, hypovitaminosis D, a term for vitamin D deficiency, has been implicated to be a potential culprit in deregulation of the immune response due to its integral role in innate and adaptive immunity (Prokopakis et al., 2013). Vitamin D, commonly known for its role in regulation of calcium within the body (Huether & McCance, 2008), is also intimately involved with immunological regulation according to Prokopakis et al. (2013). In addition to its role in the structure and function of lungs and regulation of epithelial cell immune functions, vitamin D regulates the activity of several immune cells including DCs, T and B lymphocytes, and monocytes. Furthermore, Vitamin D plays a role in adaptive immunity, specifically in T cell regulation. By decreasing Th 1 cytokine secretion and IL-2 production and increasing IL-10 production, vitamin D suppresses T-cell proliferation and, in so doing, creates a state of T regulatory cell hypo-responsiveness. In this manner Vitamin D functions in a way that mimics anti-allergy therapies, such as corticosteroids and allergy immunotherapy (Prokopakis et al., 2013).

According to Prokopakis et al. (2013), hypovitaminosis D is prevalent in western countries, affecting approximately 30% of the general adult population and 70% of the elderly or institutionalized in the West. Data on the therapeutic benefits of vitamin D

supplementation for patients with asthma and allergic disease is currently limited.

Although vitamin D seems to have therapeutic benefit for asthmatics, further research is necessary in order to demonstrate a true protective role of vitamin D against asthma and allergy development (Prokopakis et al., 2013). Nurse and other health care professionals can see hypovitaminosis D as an opportunity area for further patient teaching and education of the public as a whole as this issue clearly has far-reaching implications for population health related to both immune as well as skeletal bone health. As responsible health educators, nurses should advocate for drinking vitamin D enhanced milk, when not contraindicated, and vitamin D supplementation. When appropriate, patients may also be encouraged to have 30 minutes of unprotected sun exposure since this will activate vitamin D precursors to biologically active vitamin D. Since ability for the body to synthesize enough vitamin D through sun exposure varies widely by skin pigmentation, surface area of skin exposed, and level of sunlight, sun exposure should not be relied on as the sole means of meeting daily vitamin D requirements (Smolin & Grosvenor, 2010).

Pediatric Asthma Phenotypes

Due to its potential for allowing early interventions and improving care for pediatric patients, several longitudinal cohort studies have focused on asthma phenotypes that are most predictive of asthma development. These phenotypes have categorized pediatric patients according to onset of wheezing (Cowan & Guilbert, 2012). For example, the most well-known classification of wheezing (Cowan & Guilbert, 2012), the Tucson Children's Respiratory Study by Martinez et al. (1995), categorized 1246 newborns into four categories: never wheezing, transient early wheezing, wheezing of

late onset, and persistent wheezing. While those in the never wheezing group had never wheezed during a lower respiratory infection, those in the second classification, early transient wheezing, includes children who experienced at least one lower respiratory infection with associated wheezing that occurred before the age of three and had resolved by six years of age. In the third category, late-onset wheezing, children do not experience wheezing with a lower respiratory infection within the first three years of life, but wheezing is present at the age of six. The final category, persistent wheezing, includes children who had a lower respiratory infection with wheezing before the age of three, which continued after the age of six (Martinez et al., 1995). Several other longitudinal cohort studies have attempted to describe asthma phenotypes and have had variable results (Cowan & Guilbert, 2012). Using these phenotypes in clinical practice to determine patient's risk for asthma development is difficult due to potential for investigator bias, questions of validity, and variable age categorization of phenotypes and inconsistencies in identified risk factors (Cowan & Guilbert, 2012)

Despite numerous efforts to identify which pediatric clients with history of recurrent wheezing will eventually develop asthma, researchers still face challenges when attempting to identify clusters of symptoms that will predict future development of asthma (Cowan & Guilbert, 2012). Nevertheless, transient and persistent wheezing, atopy, diminished lung function, and infection with viruses and bacteria have all been identified as risk factors for asthma development; even so, it is still unclear which combinations of risk factors are most predictive of asthma development (Cowan & Guilbert, 2012).

Early Microbial Exposure

The early immune challenge hypothesis is an alternative interpretation of the data supporting the hygiene hypothesis (Kramer et al., 2013). This hypothesis emphasizes appropriate immune challenge early in childhood as necessary training for immune cells to recognize self from non-self-antigens (Kramer et al., 2013). Without this appropriate immunological training, the immune system is ill-equipped to recognize the body's own antigens and harmless allergens from harmful invaders, possibly laying the groundwork for the development of autoimmune disease and IgE-mediated Type I Hypersensitivities, such as asthma, allergic rhinitis, and food sensitivities (Kramer et al., 2013).

For the most part, evidence supporting the hygiene hypothesis can also be used to bolster this new hypothesis and, according to Kramer et al. (2013), may even provide more support for the early immune challenge hypothesis than the hygiene hypothesis. While decreased hygienic practices have not been found to be protective against atopy, experiencing fewer respiratory and gastrointestinal infections during childhood has been associated with a higher risk of atopy. Similarly, children residing in the country initially experience more infections early in life yet later have greater immunity to infection as evidenced by higher immunoglobulin (Ig) G levels and, at the same time, have lower incidence of asthma. Even though the incidence of infections is not increased, living in a farming environment early in life is, likewise, associated with strong protection against allergies and asthma even if the exposure occurs prenatally. This implicates that becoming infected by a microorganism is not necessarily required in order to confer

protection from asthma and allergies; rather, exposure to nonpathogenic organisms early in life can be beneficial by promoting immune system regulation (Kramer et al., 2013).

Environmental Influences

Asthma-Protective Benefits of Farming

The hygiene hypothesis is supported by evidence that microbial exposure is negatively correlated with allergies and allergic asthma but also non-allergic asthma (Brooks, Pearce, & Douwes, 2013). A cross-sectional survey of children living in Austria, Germany, and Switzerland found that exposure to animal stables and unpasteurized farm milk were strongly associated with a decreased risk of asthma, allergic rhinitis, and atopic sensitization if the exposure began early and was long-term (Riedler et al., 2001). These results have been reproduced in other studies that have found the same inverse relationship between animal contact and raw milk consumption and allergy and asthma development (Brooks, Pearce, & Douwes, 2013). There may be differences between protective benefits for allergic and non-allergic types of asthma (Brooks, Pearce, & Douwes, 2013). One of the objectives of the PARSIFAL Study team was to establish the effects of farming-related microbial exposures on asthma development (Ege et al., 2007). The result was raising pigs, feeding silage, participation in haying, consuming raw milk, and consistently spending time in animal sheds and barns were protective against asthma; however, silage was protective only for the nonatopic type of asthma (Ege et al., 2007). While children living and working on a farm generally have lower incidence of allergies and asthma, asthma risk is actually increased in children who live on farms where antibiotic-treated feed is used (Prokopakis et al., 2013).

Cleanliness and Hygienic Practices

Part of the criticism of the hygiene hypothesis has been the nomenclature of this hypothesis that may mislead healthcare consumers to believe that they should cease to practice good hygiene in their homes (Bloomfield, Stanwell-Smith, Crevel, & Pickup, 2006). For this reason, proper education of the public is necessary in order to avoid regression back to periods when illness and death were rampant due to unhygienic practices that led to rapid disease transmission within a population. According to the World Health Organization as cited in Kramer et al. (2013), transmissible diseases and mortality rates have declined in recent years due to strides made in population health, such as improved water quality, containment of sewage and other wastes, increased vaccinations, safer food preparation practices, interventions to prevent nosocomial infections, and better healthcare structures. These achievements of population health have led to significant improvement in outcomes as evidenced by doubling of the life expectancy since the year 1870. Therefore, it is important to emphasize diverse microbial exposure to harmless, nonpathogenic organisms, such as bacteria, viruses, and helminths, in natural environments in order to promote proper immune development (Kramer et al., 2013).

As affirmed by Kramer et al. (2013), standard hygienic practices should not be abandoned for the sake of increasing microbial exposure. Research actually shows that frequent hand washing with soap has little to no effect on allergic disease development. The one caveat of this is contact dermatitis, which is associated with the application of hand soaps and use of household chemicals. Even so, studies have failed to demonstrate a

connection between the prevalence of atopy and the amounts of soaps and detergents used in households (Kramer et al., 2013). In fact, the specific types of cleaners used, such as clothes washing detergent, dish detergent, toilet cleaner, and hard surface cleansers, were not individually associated with allergic diseases (Bloomfield, Stanwell-Smith, Crevel, & Pickup, 2006). These findings may be explained by the fact that the use of various cleaning methods does not significantly alter the level of microbial exposure within homes (Kramer et al., 2013). Since cleanliness has not been correlated with atopic diseases (Kramer et al., 2013), good hygiene should still be central to appropriate care and education of parents and children.

Nursing Implications

While there is clearly a protective benefit to a diversity of microbial exposures during childhood, caution must be exercised by health care professionals to not emphasize environmental exposure to the detriment of population health (Kramer et al., 2013). All relevant factors must be considered, including the developmental level of children, their immunological status, and the types of exposures that can be considered safe versus those which should be deemed potentially dangerous. The amount of available research is currently insufficient to make recommendations on specific exposures to species of microorganisms that may render protective benefits against asthma development; however, in general research has supported a negative correlation between increasing microbial diversity and incidence of allergic disease (Kramer et al., 2013).

Research supports the fact that in early childhood, especially infancy, a child's immune system is immature and vulnerable to infection (Hockenberry & Wilson, 2009). With this in mind, it is important for health care workers to emphasize appropriate hygienic practices to avoid preventable infections (Bloomfield, Stanwell-Smith, Crevel, & Pickup, 2006). Thus, prudence dictates that microbial exposures should be nonpathogenic rather than infectious since exposure to pathogenic organisms could lead to infection and associated morbidity or mortality. This is especially significant in infants since infections during infancy, instead of offering protective benefit, may actually increase the risk for atopy (Adler, 2005).

With further research, recommendations concerning lifestyle habits may also be formulated to allow for increased variety of exposure to non-pathogenic microbes in order to elicit protection against asthma development. An assessment of potential risks and benefits is, however, necessary in order to avoid encouraging unhygienic practices that may prove detrimental to population health by increasing the spread of contagious diseases (Bloomfield, Stanwell-Smith, Crevel, & Pickup, 2006). Thus, it is important to reinforce established good hygienic practices in order to protect against disease (Bloomfield, Stanwell-Smith, Crevel, & Pickup, 2006).

Asthma is one of the leading chronic illnesses of childhood, afflicting an estimated 9 million children in the United States (Lack, 2012). There is an 88% higher cost associated with hospital admission of asthmatic pediatric patients as well as longer hospital stays as compared to their nonasthmatic counterparts (The Children's Health Fund, 2006). Pediatric patients with asthma have three times as many prescriptions, twice

as many inpatient days in a hospital, and 65% more acute care visits than pediatric patients without asthma (The Children's Health Fund, 2006). Thus, it is in the best interest of patients, families, and healthcare facilities to ascertain the most effective patient and family teaching methods in order to improve care management of children with asthma and decrease the incidence of asthma exacerbations, which are costly to both families and hospitals.

Several risk factors for asthma have been identified for asthma development (See Table 1) and exacerbation (See Table 2). Identifying risk factors for the development of asthma can aid nurses in their aim to care for patients holistically. After identification of these risk factors, nurses can initiate interventions to teach patients and families about modifiable risk factors for asthma exacerbation, such as exposure to known triggers, noncompliance with medication regimen, lack of knowledge regarding disease management, and lack of specialty care (Schatz, 2012). Since patient teaching is one of the key roles of nurses (Lahl, Modic, & Siedlecki, 2013), nurses should not only teach parents about risk factor reduction but also how to recognize symptoms of acute exacerbations, such as wheezing, difficulty breathing, nasal flaring, and retractions (Hockenberry & Wilson, 2009).

Table 1: *Risk Factors for Asthma Development*

Host Factors	Environmental Factors
Age	Inadequate bacterial antigen exposure
Gender	Environmental pollution
Race	Urban and rural residence
Parents with allergy	Country or continent of residence
Twin siblings with allergy 70% with monozygotic 15% with dizygotic	Higher environmental allergen exposure Household dust mites and mold Pollen and diesel soot

(Kramer et al., 2013)

Table 2: *Risk Factors for Asthma Exacerbation*

Modifiable Risk Factors for Exacerbation
Exposure to known triggers
Noncompliance with medication regimen
Knowledge deficit regarding disease management
Inadequate access to specialty care

(Schatz, 2012)

Evidence shows that patients and families should be provided with written asthma action plans (WAAP) (Marshall, Asperen, Selvadurai, & Robinson, 2013). The WAAP provided to patients and families typically has three sections; the first outlines how to recognize the symptoms of an asthma attack; the second describes the appropriate situation-based treatments, and the third elucidates when it is necessary to seek

emergency care (Tan, Chen, Soo, Ngoh, & Tai, 2013). In this way, WAAPs reinforce patient teaching and self-management at every stage of care (McCarty & Rogers, 2012). In addition to providing information on the symptoms of an attack, some WAAPs provide specific guidelines for interpreting peak flow meter readings and guidelines for titrating medication dosages (McCarty & Rogers, 2012). Asthmatics should be taught to routinely check peak flow meter readings since they reflect lung capacity, a measure which decreases in an acute asthma attack as a result of bronchospasm (Peak flow meter, 2010). These peak flow readings can help indicate the appropriate treatment and whether rescue bronchodilators are necessary (Peak flow meter, 2010). Providing patients and families with a customized WAAP, thus, not only increases confidence in their ability to manage care but also increases understanding and recognition of symptoms (Marshall, Asperen, Selvadurai, & Robinson, 2013).

When evaluating teaching and disease management guidelines, one must remember that written instructions do not replace good patient teaching. For this reason, nurses should take an interactive teaching approach while teaching symptom identification, medication information, disease management, and recognition of an asthma exacerbation and appropriate treatment. This is vital because patients and families need to understand when to seek acute care in an Emergency Department or call 911 for Emergency Medical Services (Lack, 2012). For example, nurses should teach patients that when removing the trigger and taking appropriate prescriptions does not resolve the symptoms of the asthma attack, it is time to seek professional acute care immediately in order to avoid further escalation of the attack and progressive bronchoconstriction.

With recent health care reform, nurses' roles in after-hospital care are expanding as more emphasis is placed on the continuum of care (Harkness & DeMarco, 2012). A smooth transition to outpatient care can be facilitated by making appropriate referrals and connecting families to community resources (Harkness & DeMarco, 2012), and providing families with educational materials suited to their needs (Lahl, Modic, & Siedlecki, 2013). In addition to teaching asthmatic patients and families how to manage daily care, nurses also need to teach parents when to bring their child in to the Emergency Department or call 911 and how to handle pre-hospital emergent care of their child (McCarty & Rogers, 2012). Pediatric and Emergency Department nurses are responsible for ensuring that their patients will be safe during their stay in the hospital and that family members have sufficient understanding of disease processes to provide quality care after discharge (Harkness & DeMarco, 2012). Emergency Department nurses play a vital role in patient teaching after an acute exacerbation (Lack, 2012). In addition to providing standard discharge teaching, the rate of completed follow-up was higher when emergency nurses aided families in setting up necessary outpatient follow-up appointments instead of simply providing the standard written instructions for following up with a primary care provider (Lack, 2012).

Care must be taken in patient education to ensure that parents have correct understanding of the information so that they may be able to use it appropriately. Prior to discharge, nurses are responsible for ensuring patient and family understanding of appropriate self-care and disease management (McCarty & Rogers, 2012). Patients and caretakers should verbalize understanding of how to avoid known triggers, proper use of

inhalers, and the purpose and use of daily medication and rescue bronchodilators (McCarty & Rogers, 2012). Nurses can use the teach-back method to evaluate patient understanding by asking open-ended statements such as “Tell me what we have talked about today, as you understand it?” (Oates & Silliman, 2009, p. 379). These conversation openers enhance communication between the patient, family, and nurse by allowing patients and families to clarify their knowledge and nurses to determine whether teaching was effective (Oates & Silliman, 2009). Patient teaching and verbalization of understanding should also be appropriately documented according to institutional policy.

Patient teaching in the hospital from emergency and pediatric nurses should be reinforced by school nurses in the outpatient setting. As case managers, school nurses have a unique opportunity to coordinate patient care, monitor patient health status, and continue disease management teaching on a weekly basis (Lack, 2012). Implementation of these interventions by school nurses on a weekly basis can not only decrease the number of days children with asthma are absent from school but also decrease the frequency of asthma-related Emergency Department visits and reduce the number of days this population stays in the hospital (Levy, Heffner, Stewart, & Beeman, 2006).

Directions for Further Research

In the future, understanding the relationship between infection and atopy may provide insight into new treatment modalities for patients with hypersensitivity reactions. Knowledge of the precise mechanism underlying the negative association between infection and allergic disease may also increase the effectiveness of current treatment modalities such as allergy shots. Since knowledge of the complex interplay of factors

affecting immunity and hypersensitivity remains incomplete, medical professionals are currently unable to make recommendations for preventing atopy. For this reason, there is a need for further research in this area in order that recommendations for asthma prevention may be identified and utilized in both the home and the healthcare setting (von Mutius, 2007).

Several studies have demonstrated protective benefits of children living on a farm (Kramer et al., 2013). Living in a rural setting is also associated with protection against atopy because of increased exposure to endotoxins (Prokopakis et al., 2013). Further research is needed in order to determine whether or not time in the countryside would be beneficial for urban-dwelling children. While early and ongoing exposure would be needed to protect against asthma development (Brooks, Pearce, & Douwes, 2013), in theory, repeated exposures to the same types of organisms encountered by farm-dwelling children could have the same benefits. Caution certainly must be exercised in children who are already sensitized to environmental allergens found on a farm, such as pollen and hay, since this may stimulate airway inflammation and cause an asthma attack (Huether & McCance, 2008). Further research is needed to determine whether short visits to rural, farming communities offers the same protective benefits as living on a farm.

Owning a pet may, similarly, offer protective benefits since pet ownership has been associated with increased microbial exposure as the pet carries microorganisms from outdoors into the home environment (Heederik & von Mutius, 2012). Further research, however, is necessary to determine whether there is a potential advantage to pet ownership. Caution should be exercised here too since many children can become

sensitized to their own favorite pets. In this case, pet exposure could be potentially dangerous if it leads to status asthmaticus. Since hypersensitivities are often cumulative in their development, that is they increase with each exposure, parents should be educated about the signs and symptoms of asthma development such as wheezing and difficulty breathing (Huether & McCance, 2008).

As pointed out by Kramer et al. (2013), recent research indicates that the increased incidence of atopy may be attributable to the modern lifestyle, not just lack of diverse microbial exposure in the early years of childhood immune development. In recent decades exposure to allergens, which are capable of exacerbating or initiation an asthma attack, has increased. In addition, environmental changes have led to an increase in the baseline total allergy load affecting the population living in industrialized nations. These changes include diminished ventilation in residential dwellings, increased relative humidity which increases mold growth, higher exposure to pollutants present in building materials, increased preservatives added to foods and other consumable substances, and greater utilization of antibiotics; these may all work together to contribute to the problem of asthma pathophysiology and exacerbation (Kramer et al., 2013). Further research is necessary to elucidate whether modifying specific risk factors, such as pollutants in building materials, repeated exposures to antibiotics, and preservatives in foods, could lower the risk of allergy and asthma development in the general population.

The field of clinical immunology is rapidly expanding as new knowledge is gained with the ever increasing body of research. As competent clinicians seeking to meet patient healthcare needs with evidenced-based practice, nurses need to stay abreast

of the current findings affecting their practice. The field of immunology, and specifically research surrounding the hygiene hypothesis, offers great opportunity areas for further evidenced-based nursing research. Hopefully, with this type of clinical research, evidenced-based protocols could be formulated, implemented, and evaluated for the improvement of pediatric asthmatic client care and teaching.

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