Role of airway microbe in development of pediatric asthma: a systematic review

Nourhan Waleed Jastaniah1*, Nouf Aljehani2

ABSTRACT

According to the literature, there is evidence of an association between the development of asthma and the microbiome. Here, this systematic review aimed to study the role of microbes in developing pediatric asthma. This systemic literature review was conducted comprehensively on the PubMed database between 2013 and June 2023 to explore the role of airway microbiome in developing pediatric asthma. The general search keywords used were: [(Asthma) AND (children)] AND (Airway microbiome). The inclusion criteria were sufficient details on the role of airway microbiome in developing pediatric asthma. Meanwhile, the exclusion criteria were studies discussing the role of airway microbiome in developing pediatric asthma in adults, case reports, letters, reviews, and studies published in languages other than English. Our search identified 34 articles obtained from the PubMed database. After the full-text inspection, only five studies met the inclusion criteria for the systematic review. The sample size of the study subjects was 679 children ranging from 0 to 16 years. The study designs included integrated clinical, systematic integrative, prospective observational, and cohort studies. Microorganisms were detected from the nasopharyngeal, nasal, bronchial airways, oropharynx, hypopharynx, and nostrils. Regarding the detected microbes, Staphylococcus aureus was detected in one study, Streptococcus in two studies, and Streptococcus pneumoniae and Moraxella catarrhalis were found in two studies. The review concluded that bacterial infections, particularly those caused by Streptococcus pneumoniae, Haemophilus influenzae, M. catarrhalis, and viral infections (mainly rhinovirus and respiratory syncytial virus), have been associated with increased asthma development among children. Further studies are needed to understand microbial infection mechanisms for developing pediatric asthma.

Keywords: Asthma, pneumonia, pediatrics, microbes, viral infections, bacterial infections.

Introduction

Asthma is a complex and diverse disease characterized by chronic airway inflammation [1]. Currently, over 300 million people worldwide are estimated to be affected by asthma, and the incidence of it continues to rise. The prevalence of asthma globally is variable, ranging from 1% to 20% in children and adults. Over the past three decades, studies conducted on Saudi children have reported asthma prevalence rates ranging from 8% to 25%. The symptoms mainly involve the narrowing and inflammation of the airways, which are thought to result from a combination of genetic and environmental factors. In children, the development of asthma is linked to various factors, including delivery by cesarean section, antibiotic use during the neonatal period, a maternal diet low in fiber, formula feeding with milk, and exposure to different environmental microbes [2–4]. Asthma can range from mild to severe and can exhibit varying activity levels, onset times, and responses to treatments. There is an ongoing debate about whether asthma is one disease or a spectrum of related but distinct conditions [5]. Recent research has led to categorizing asthma into separate phenotypes, further divided into several endotypes [5].

Previous research has identified multiple factors that increase the risk of persistent wheezing in children [5–6]. Atopy may contribute to the persistence of challenging asthma [7], while differences in inflammatory pathways could explain the progression from early airway inflammation to the substantial airway remodeling observed in individuals with persistent asthma [5].

Correspondence to: Nourhan Waleed Jastaniah
*Pediatric Specialist, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia
Email: nounz_jay@windowslive.com
Full list of author information is available at the end of the article.
Received: 23 June 2023 | Accepted: 29 July 2023
Table 1. Main characteristics of the included studies.

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Study design</th>
<th>Study subjects, sample size</th>
<th>Age</th>
<th>Microorganism colonization</th>
<th>Microorganisms detected</th>
<th>Findings</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raita et al. [6]</td>
<td>Integrated clinical study</td>
<td>221 Infants hospitalized with RSV bronchiolitis</td>
<td>&lt;1 year</td>
<td>Nasopharyngeal airway</td>
<td>Streptococcus pneumoniae/Moraxella catarrhalis, and RV coinfection</td>
<td>A high proportion of IgE sensitization and high IFN-α and -γ response</td>
<td>They found that infants with a high proportion of IgE sensitization and high IFN-α and -γ response accompanied by infection had a significantly higher risk for developing asthma.</td>
</tr>
<tr>
<td>Chun et al. [7]</td>
<td>A systematic, integrative study</td>
<td>27 Children with severe persistent asthma and 27 healthy control children</td>
<td>Children with severe persistent asthma had a median age = 11 years, and healthy control children had a median age = 13 years</td>
<td>Upper (e.g., nasal) and lower (e.g., bronchial) airways</td>
<td>Moraxella, Alloiococcus, Actinomyces, Corynebacterium, Staphylococcus, and Staphylococcus</td>
<td>Some types of nasal microbes, such as Corynebacterium, were negatively associated with more nasal genes for inflammation in healthy versus asthmatic children</td>
<td>There was an association between the nasal and bronchial microbiome in children with severe persistent asthma and healthy controls.</td>
</tr>
<tr>
<td>Zhang et al. [8]</td>
<td>A prospective observational study</td>
<td>74 Infants who were hospitalized as a result of severe RSV bronchiolitis</td>
<td>≤6 months</td>
<td>Nostril</td>
<td>Streptococcus, Haemophilus, Moraxella, Prevotellaceae, and Clostridiales</td>
<td>Airway levels of Lipopolysaccharides, CXCL8, CCL5, IL-6, and IL-13 were significantly higher in infants who later developed recurrent wheezing than those who did not. Higher abundance of Haemophilus and Moraxella in the airway, contributing to subsequent recurrent wheezing in later childhood.</td>
<td>The relative abundance of detected bacteria was higher in infants who developed recurrent wheezing than in those who did not. Higher abundance of Haemophilus and Moraxella in the airway, contributing to subsequent recurrent wheezing in later childhood.</td>
</tr>
<tr>
<td>Cuthbertson et al. [9]</td>
<td>Cohort</td>
<td>109 Children with acute wheezing</td>
<td>From 0 to 16 years</td>
<td>Oropharynx</td>
<td>RV, RSV, Coronavirus, Human metapneumovirus, Adenovirus, Enterovirus, Bocavirus, Paramyxovirus, and bacteria.</td>
<td>-</td>
<td>Wheezing and viral infection did not associate with the bacterial community significantly. The bacterial airway microbiome’s role in wheezing was less clear than viral influences.</td>
</tr>
<tr>
<td>Rahman Fink et al. [10], Zealand and Denmark</td>
<td>Cohort</td>
<td>248 Children of asthmatic mothers</td>
<td>1 month</td>
<td>Hypopharynx</td>
<td>Moraxella catharralis, Haemophilus influenzae, and/or S. pneumonia</td>
<td>hs-CRP, TNF-α, and IL-6 confirmed an inflammatory profile among children colonized with Moraxella catharralis, Haemophilus influenzae, and/or S. pneumonia in the hypopharynx</td>
<td>The microbiome in the upper airway in early life could cause low-grade systemic inflammation.</td>
</tr>
</tbody>
</table>

*hs-CRP: High-sensitivity C-reactive protein
*IL: Interleukin
*RSV: Respiratory syncytial virus
*RV: Rhinovirus
*TNF: Tumor necrosis factor.
The human body is considered a home of many microorganisms, including bacteria, viruses, and fungi, which reside on both its internal and external surfaces. Evidence suggests that colonizing mucosal tissues by microbes during infancy plays a critical role in developing, maintaining, and regulating the immune system [5]. Imbalances in microbial populations, known as dysbiosis, particularly in the gut microbiota, have been linked to the development of various illnesses, including asthma and allergic diseases. The lung was believed to be sterile for a long time, but numerous publications have reported that it harbors its own microbiota [6,7]. As a result, dysbiosis in the lung microbiota may also play a role in developing respiratory disorders like asthma.

Variations in the airway microbiota may be associated with physicochemical property gradients within airway microhabitats. Bacterial structural ligands have also been shown to regulate host immune responses within the respiratory tract. The changes in the airway microbiome can differ according to age and disease status [6,7]. Studies have found that certain bacteria within the *Haemophilus*, *Moraxella*, and *Neisseria* genera are consistently more abundant in severe or childhood asthma cases [6]. In addition, recent findings indicate that the initial interactions between respiratory microbiota and viruses may impact host immune responses, potentially influencing the pathogenesis, severity, and outcomes of acute respiratory tract infections, particularly in relation to asthma [6,7]. Furthermore, this systematic review aimed to study the role of microbes in developing pediatric asthma.

**Literature Search**

This systematic literature review was conducted on the PubMed database between 2013 and June 2023 to investigate the role of the airway microbiome in the development of pediatric asthma. The search utilized the following general keywords: [(Asthma AND (children))] AND (Airway microbiome). All study titles and abstracts resulting from this search were screened systematically. Subsequently, the results were filtered to include only original research articles that defined the role of the airway microbiome in pediatric asthma development. Further refinement was done by filtering the selected trials to include studies focusing on pediatric patients between 2013 and June 2023. Only studies available in English were considered for evaluation in the second step. The subsequent stage involved determining and applying the inclusion criteria to select studies for review. The inclusion criteria centered on studies providing sufficient details about the role of the airway microbiome in the development of pediatric asthma. Meanwhile, the exclusion criteria were set as follows:

1. Studies discussing the role of the airway microbiome in developing pediatric asthma in adults.
2. Any case reports, letters, and reviews.
3. Studies published in languages other than English.

The abstracts were carefully checked manually to identify and select the appropriate ones to be included in the review. By adhering to this comprehensive and systematic process, the literature review aims to contribute valuable insights into the role of the airway microbiome in pediatric asthma development based on the selected studies.

Lastly, the essential data were retrieved from the final record of included studies to be summarized. The data extracted from the included studies were the following variables: the authors, years and country of the study, the study design, the study subjects and sample size, the age of the included populations, the microbiome detected, findings, and outcome. No informed consent was required as the review does not contain participants’ interventions.

**Results**

Our search identified 34 articles obtained from the PubMed database. After the full-text inspection, 29 studies were excluded from the current study; 11 were reviews, and 18 did not meet the study objective. Therefore, only five studies met the inclusion criteria for the systematic review. The sample size of the study subjects was 679 children ranging from 0 to 16 years. The study designs included integrated clinical, systematic integrative, prospective observational, and cohort studies. Microorganisms were detected from the nasopharyngeal, nasal, and bronchial airways, oropharynx, hypopharynx, and nostrils.

Regarding microbes, *Staphylococcus aureus* was detected in one study, *Streptococcus* was detected in two studies, and *Streptococcus pneumonia* and *Moraxella catarrhalis* were found in two studies. On the other side, rhinovirus (RV) infections were most common among the patients and were found in two studies, while respiratory syncytial virus (RSV) infection was in only one study. A summary of the characteristics and results of included studies is illustrated in Table 1.

**Discussion**

Respiratory infections are among the primary causes of disease morbidity globally, with infectious agents as the primary cause of mortality in lung disease. In the past 30 years, respiratory infections have consistently been identified as the main factor triggering asthma exacerbations in children and adults. These exacerbations can range from mild to severe, resulting in bronchitis, wheezing, or lower respiratory airway pneumonia [11]. This systematic review aimed to study the role of microbes in developing pediatric asthma.

Asthma is always characterized by the presence of T helper 2 airway immune cells, such as allergen-specific IgE production by plasma cells and eosinophils [11]. In addition, high biomarker levels, such as high-sensitivity C-reactive protein (hs-CRP), may be associated with low-grade systemic inflammation [23]. According to the included studies, Raita et al [19]. reported...
Airway microbes & pediatric asthma: a systematic review

227 and viral infections contributed to the development
225 of IgE sensitization, high IFN-α, and -γ response by
224 infection had a significantly higher risk for developing
223 asthma. On the other hand, Rahman Fink et al. [23],
222 determined low-grade systemic inflammation in the
221 included subjects by measuring plasma levels of hs-CRP,
220 TNF-α, and interleukin-6 (IL-6). Furthermore, Zhang et
219 al. [21] found that IL-6 and IL-13 were higher in infants
218 with recurrent wheezing. Several bacterial and viral
217 agents can induce similar asthmatic symptoms in young
216 children [11]. Regarding the most common bacteria
215 causing asthma, S. aureus and/or its enterotoxins are
214 considered risk factors for the development and
213 severity of asthma [11]. Other respiratory bacteria have
212 been identified to cause severe persistent wheezing
211 in children, such as Streptococcus pneumoniae,
209 In the current systematic review, S. aureus was detected
208 in one study [20], and Streptococcus was detected in
207 two studies [20,21], in addition, S. pneumonia and M.
206 catarrhalis were found in two studies [19-23]. Viral
205 coinfections are usually found in up to 30% of children
204 who suffer from acute respiratory tract infections [11].
203 There is strong evidence that respiratory viruses have
202 an important role in developing asthma in children.
201 Previous studies showed that RSV bronchiolitis, which
200 is severe enough to require hospitalization, is a risk
199 factor for asthma at ages 7, 13, and 18 [11]. Furthermore,
198 it was detected that wheezing illnesses associated with
197 RV infections in early childhood are a strong predictor
196 of asthma development. Regarding the included studies,
195 RV infections were most common among the patients
194 and were found in two studies [19-22], while RSV
193 was in only one study [22]. The epithelial cells are the
192 principal site of virus infection, especially RV in both
191 the upper and lower airways; on the other side, virus-
190 induced alterations of epithelial cells play a significant
189 role in regulating clinical outcomes [30]. The detected
188 viruses were found in the nasopharyngeal airway and
187 oropharynx. Evidence suggests that early interactions
186 between respiratory microbiota and viruses could
185 modulate host immune responses, potentially affecting
184 acute respiratory tract infections’ pathogenesis, severity,
183 and asthma-related outcome [21]. A study indicated that
182 a higher abundance of Haemophilus and Moraxella in
181 the airway might modulate airway inflammation during
180 severe RSV bronchiolitis in infancy and contributed to
179 subsequent recurrent wheezing in later childhood [21]
178 Raita et al. [19] found that infants with a high proportion
177 of IgE sensitization and high IFN-α and -γ response
176 accompanied by infection had a significantly higher risk for developing asthma. However, Cuthbertson et
175 al [22] found that wheezing and viral infection did not
174 associate with the bacterial community significantly.
173 Furthermore, the current review indicated a lack of
172 data related to the exact mechanisms by which bacterial
171 and viral infections contributed to the development
170 of asthma. The characterization of these mechanisms
169 might have a valuable impact on the understanding of asthma development.

Conclusion

The review concluded that bacterial infections, particularly those caused by Streptococcus pneumoniae,
Haemophilus influenzae, M. catarrhalis, and viral infections (mainly RV and RSV), have been associated
with increased asthma development among children. The exact mechanisms by which bacterial and viral infections
contributed to the development of asthma were not fully understood. Overall, these findings highlight the potential
for preventative and therapeutic strategies that target the microbiome and respiratory infections to reduce the
burden of asthma. However, further studies are needed to understand better microbial infection mechanisms
regarding developing pediatric asthma.

List of Abbreviations

CRP C-reactive protein
IFN-α High tumor necrosis factor
IL-6 Interleukin-6

Conflict of interest

Not applicable.

Funding

None.

Consent to participate

Not Applicable.

Ethical approval

Not applicable.

Author details

1. Nourhan Waleed Jastaniah, Nouf Aljehani
2. Pediatric Specialist, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia
3. King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia

References

Airway microbes & pediatric asthma: a systematic review


