Int.J.Curr.Microbiol.App.Sci (2022) *11*(06): 1-9

International Journal of Current Microbiology and Applied Sciences
***ISSN: 2319-7706* Volume 11 Number 06 (2022)**
Journal homepage: http://www.ijcmas.com

Review Article https://doi.org/10.20546/ijcmas.2022.1106.001

Bacterial Pathogens and Bronchial Asthma: A Review

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Keywords

Asthma, bacteria, exacerbation, immune response. microbiome, respiratory tract infections

Article Info

Received:
02 May 2022
Accepted:
30 May 2022
Available Online:
10 June 2022

A B S T R A C T

Bronchial asthma is a chronic respiratory disorder influenced by both genetics and environmental factors. The pathology of asthma is characterized by an increased influx of TH2 cells, eosinophils, increased circulating immunoglobulin E (IgE) and mucus hypersecretion in the airways. A respiratory bacterial infection in early childhood is closely associated with the development of bronchial asthma, and also the greatest contributing factor to asthma exacerbation in both children and adults. Typical and atypical bacterial species that have been linked with asthma exacerbations include *Haemophilus influenza, Streptococcus pneumoniae, Mycoplasma pneumoniae and Chlamydia pneumoniae*. Moreover, microbiome compositions and particular imbalances in respiratory flora are also responsible for asthma exacerbations early in life and play a significant role as a determinant of respiratory health and potential asthma development. This reviews highlights on the role of respiratory microbiome and bacterial pathogens in triggering the immune response resulting in asthmatic attacks and exacerbations.

Introduction

Asthma is a chronic respiratory disease characterized by episodes of shortness of breath and wheezing due to reduced airway flow in terminal and smaller bronchial airways of the lung. It is triggered by a hyperactive immune response to allergens, leading to hyper inflammation, mucus production, changes in structural cells lining the airways, and airway hyper responsiveness (Huang *et al.*, 2015). The development of asthma is influenced by genetics and environmental factors in both in utero and postnatal (Mthembu *et al.*, 2021). Environmental factors include microorganisms whether bacterial, fungal or viral; or air pollutants, aeroallergens and food (Schwarze *et al.*, 2002). Although asthma, is present in adults, it is considered as a childhood condition. Respiratory infections are the greatest contributing factor to asthma exacerbation in both children and adults. The severity and frequency of exacerbations varies from mild to severe bronchiolitis, wheezing, or

pneumonia in the lower respiratory airway (Khetsuriani *et al.*, 2007).

Pathophysiology of Asthma

Respiratory epithelial cells are constantly exposed to many types of challenges, including pathogens, allergens and environmental pollutants (Lee *et al.*, 2021).

Consequently, they are able to respond quickly and effectively to cellular damage such as the local cytokine production, lateral transport by ion exchanges, wide arrays of mucus compositions, secretion of antimicrobial peptides, and epithelial shedding. The airway epithelium is thus a central part of the local immune response and bridges innate and adaptive immune functions against all types of foreign bodies entering the respiratory system (Calvén *et al.*, 2020).

Therefore it plays a critical role in the development as well as in the progression and exacerbation of the asthma. Hence, a disturbed cellular barrier enables allergens to enter the body and to induce a sensitization reaction, which is widely regarded as the starting point of an asthma (Frey *et al.*, 2020).

When the protective epithelial layer and mucous act as physical barriers, they become compromised and the release of pathogens deterring molecules such as secretory immunoglobulins becomes impaired (Frey *et al.*, 2020; Xiang *et al.*, 2022).

As a consequence, this defensive frontline is breached and airway epithelial cells are infected and even destroyed by respiratory pathogens. A vicious cycle is started where barrier disturbance and infection promote each other (Frey *et al.*, 2020). The pathology of asthma is characterized by an increased influx of TH2 cells, eosinophils, increased circulating immunoglobulin E (IgE) and mucus hypersecretion in the airways (Kudo *et al.*, 2013). Increased production of type 2 cytokines leads to allergen triggered IgE hypersensitivity and activation of mast cells, basophils, eosinophils, airways epithelial cells, and remodeling of airways. It is thereby associated with atopic disease; allergy, allergic rhinitis, and asthma (Hüls *et al.*, 2019).

Asthma comprises distinct mechanistic pathways (endotypes) with variable clinical phenotypes (childhood atopic, non-atopic, middle-aged obese, and elderly late-onset). The chronic inflammation of the conducting airways is different in various asthma endotypes namely Th2 high (atopic, eosinophilic) and Th2 low (non-atopic, non-eosinophilic) endotypes. Th2 cells mainly secrete inflammatory cytokines such as IL-4, IL-5, and IL-13 that stimulate Th2 type immunity characterized by eosinophilia and high antibody titers (IgE-producing B cells) (Peters *et al.*, 2014; Bush, 2018).

Role of Bacterial Pathogens in Bronchial Asthma

Respiratory bacterial infections have emerged as a major predictive factor in developing wheezing at an early age. The detection rates of these infectious agents are highest among colonization with pathogenic bacteria could lead to chronic lower airway inflammation, impaired mucociliary clearance, increased mucous production and eventually asthma (Leung *et al.*, 2017).

Bacterial components

Bacterial components as endotoxins and flagellin demonstrate contradictory effects on asthma. Endotoxins are lipopolysaccharides (LPS) derived from the cell wall of Gram negative bacteria; are found in both outdoor and indoor environments, where the main source of these molecules are livestock and pets. Endotoxins derived from farm animals have been associated with a decrease in asthma development in children (Stein *et al.*, 2016; Beigelman *et al.*, 2016).

On the other hand endotoxins are induce an immune response that has been implicated in the development of allergic diseases including asthma (Thorne *et al.*, 2005). The lipid A portion of endotoxins triggers cytokine production and cellular

responses. However, responses following endotoxin exposure are postulated to be dose dependent, where a low dose will provide protection to infectious agents while a high dose may elicit a detrimental immune response (Williams *et al.,* 2005).

Another bacterial component, flagellin, is a protein commonly found in Gram negative bacteria. It is known to be a potent mucosal immune cell activator (Hajam *et al.,* 2017). Similar to LPS, it plays a conflicting role in asthma. Some authors reported flagellin to suppress and regulate allergic responses by, while others have associated it with inflammatory responses that trigger asthma (Shim *et al.,* 2016; Zakeri *et al.,* 2018; Whitehead *et al.,* 2020; Mthembu *et al.,* 2021).

Bacterial Agents

Bacterial respiratory infection in early childhood is closely associated with asthma development. Moreover, bacterial colonization plays an important role in disease exacerbations. Bacterial species that have been linked with asthma exacerbations include *Haemophilus influenza* (*H. influenzae*), *Streptococcus pneumoniae* (*S. pneumoniae), Mycoplasma pneumoniae (M. pneumonia) and Chlamydia pneumoniae* (*C. pneumoniae*) (Toews, 2005; Peng *et al.,* 2019).

Haemophilus influenza

H. influenza is a Gram-negative bacterium whose species are classified according to the presence or lack of the polysaccharide capsule. Only one group of encapsulated type referred to as non-type able *H. influenzae* is implicated in various inflammatory disease exacerbations (Langereis *et al.,* 2015).

H. influenzae naturally, forms part of upper respiratory tract microbiome. Colonies are detected within the first year of life, and progressively expand through adulthood; and were found to predominate individuals with asthma. *H. influenzae* is implicated in the inception of asthma as well as its exacerbation. It has the ability to attach on several receptors of the airway epithelium, thus facilitating augmented inflammatory responses. It is among the 5 mostly frequently detected pathogenic bacteria in children and is a common feature of neutrophilic asthma (Langereis *et al.,* 2015; Simpson *et al.,* 2016).

H. influenzae promotes a predominant neutrophilic inflammation through the induction of interleukin-17(IL-17). This leads to the suppression TH2 responses, consequently propelling the development of non-controllable asthma. Moreover, the long term exposure to *H. influenzae* has been proved to trigger a TH17-dependentneutrophilia with subsequent defective regulatory T cells (Tregs) response, leading to chronic inflammation and airway remodeling. This form of asthma in children is usually unresponsive to treatment (Yang *et al.,* 2018).

Streptococcus pneumoniae

S. pneumoniae is a Gram-positive bacteriumen capsulated by polysaccharides. The bacteria normally colonizes the upper respiratory tracts and exist as a commensal organism in healthy hosts (Otero *et al.,* 2013). Several studies have associated *S.pneumoniae* colonization with allergic airway disease (Roberts *et al.,* 2019; Castro-Rodriguez *et al.,* 2019; Henares Desirée *et al.,* 2021).

Infants, who later developed asthma, had an immune response to *S. pneumoniae* with increased interleukin 5 (IL-5) and IL-13and decreased IL-17 and IL-10. (Larsen *et al.,* 2014) Further data in young children has shown that colonization with *S. pneumoniae* can contribute to the severity of asthma exacerbations. (Kloepfer *et al.,* 2014)Not only does colonization with *S. pneumoniae* predispose children to wheezing but there are also implications for asthma development propelled by bacterial infection (Weiser *et al.,* 2018).

However *S. pneumoniae* also poses an immunoregulator protective effect that may be used for therapeutic purposes (Kama *et al.,* 2020). When

asthmatic children are vaccinated with pneumococcal vaccine, the incidence of asthmatic attacks were found to decrease (Eisenlohr *et al.*, 2020).

S. pneumoniae confers protection against the development and progression of asthma through the suppression of both TH1 and TH2 responses, reduction of airway inflammatory cell recruitment and airway obstruction. An inverse correlation between the intensity of symptoms experienced by individuals during an asthma attack and *S. pneumoniae* colonisation has been reported, where tumour necrosis factor –alpha (TNF-) acts as the immunoregulator of *S. pneumoniae* inducing a protective effect (Kama *et al.*, 2020).

Chlamydia pneumoniae

C.pneumoniae is an intracellular Gram-negative atypical bacteria mainly infecting epithelial cells, endothelial cells and monocytes and macrophages. *C. pneumoniae* infection has been reported as a possible etiologic agent in asthma since Hahn *et al.*, 1991 showed an association between *C. pneumoniae* serology and asthma. Subsequent studies have demonstrated that *C. pneumoniae* infection caninitiate and exacerbate asthma, especially in adults where this may contribute to chronic asthma symptoms in some patients (ELAkkary *et al.*, 2017; Endo *et al.*, 2017; Webley and Hahn, 2017).

C.pneumoniae has also been shown to induce secretion of TNF-alpha and IL-8. Paróczai *et al.*, 2020). It has been suspected to contribute to airway remodeling by inducing the production of IL-6, IFN-Beta and MMPs that can promote smooth muscle cell proliferation. Moreover, it poses the ability to impair apoptosis of infected cells leading to chronic infection and to induce ciliostasis in the bronchi (ELAkkary *et al.*, 2017).

Failure to eradicate *C. pneumoniae* can lead to chronic infection, where *C. pneumoniae* enters a state of "latency" in which it is viable but dormant and does not multiply. It however continues to synthetize heat shock protein 60, able to induce a strong inflammatory response and may have intermittent periods of replication (Calmes *et al.*, 2021).

The diagnosis of acute *C. pneumoniae* infection is usually based on serologic criteria that include the presence of IgM antibodies and/or rise in IgG antibodies. The absence of an increase in IgM suggests reinfection rather than primary infection. Reinfection or reactivation of *C. pneumoniae* infection is followed by elevated IgG antibody levels that persist for months or years, whereas IgA levels decay much more rapidly. For this reason, IgA antibody is considered a more reliable marker for chronic *C. pneumoniae* infection (Kumar and Hammerschlag, 2007). Patients with IgA and IgG against *C. pneumoniae* have more severe disease with increased airway obstruction, higher doses of inhaled corticosteroids, more signs of air trapping and less type-2 inflammation (Endo *et al.*, 2017; Calmes *et al.*, 2021).

Calmes *et al.*, 2021, reported in their study that 65% of asthmatics had signs of past exposure and 17% had signs of chronic infection to *C. pneumoniae*. Most of their IgA+ /IgG + patients had moderate or severe asthma and were treated with higher doses of inhaled corticosteroids. Higher doses of inhaled corticosteroids may modify the local immune responses by reducing cytokine production in the lungs by effector T-cells and also decrease eosinophils. However it may affect the host's ability to eradicate intracellular pathogens by down regulating Natural Killer cell activity and IL-12, IL-10 and TGF-Beta production by macrophages. Higher doses of may however also be a consequence of poorer asthma control due to chronic *C. pneumonia* infection.

Mycoplasma pneumoniae

M. pneumonia, an extracellular atypical bacteria lacking a cell wall, is a common causative agent of pneumonia in children and young adults. The mechanism of *M. pneumoniae* pathogenesis lies

upon the induction of various cytokines and chemokines (He *et al.,* 2016).

Host immune factors may influence the outcome of infection, and previous findings showed that asthmatic children were lacking in cellular and humoral responses to *M. pneumoniae* infection. It causes infection in the upper and lower respiratory tract, causing pneumonia or bronchitis, and may be involved in the initiation and recurrence of asthma exacerbations (Watanabe *et al.,* 2014; Yin *et al.,* 2017). It has been suggested that *M. pneumoniae* infection leads to changes of a variety of serum immune parameters, such as *M. pneumoniae* immunoglobulins M and E, interleukin-18 and eosinophilic count (Yeh *et al.,* 2016).

A study found that *M.pneumoniae* - IgM levels were higher in asthmatic children when compared with healthy controls, indicating that elevated *M.pneumoniae*-IgM levels may be involved in the development of asthma among children. As a specific antigen, *M.pneumoniae* can induce immediate or delayed hypersensitivity reaction, and may result in allergic airway inflammation and with the production of IgE and IgM. This may mediate type 1 hypersensitivity reaction and thereby *M.pneumoniae* may lead to the development of asthma as well as their exacerbations. High positive levels of *M.pneumoniae*-IgM antibodies were found in patients who were infected with *M.pneumoniae* during asthma exacerbation (Yin *et al.,* 2017; Elzawawy *et al.,* 2020).

These results were supported by Kassisse *et al.,* 2018 who confirmed that children with acute asthma show a high prevalence (46%) of *M.pneumoniae* infection and there is a close relation between severe acute asthma exacerbation and the presence of *Mycoplasma pneumoniaee*. Also, Iramain *et al.,* 2016 suggested that there are association between acute infection of *M.pneumoniae* with severe asthma attack in children, the prevalence of *M.pneoniae* was significantly higher among children with severe asthma as compared to children with moderate asthma and control groups.

Microbiome and Bronchial Asthma

The microbiome is a significant part of our defense system made up of a community of commensal microorganisms whose main responsibility is to maintain immune homeostasis (Berg *et al.,* 2020). However, an occasional imbalance in the microbiome occurs in certain individuals, triggering an intense immune response leading to several immune disorders. Certain microbiome compositions and particular imbalances in respiratory flora are responsible for asthma exacerbations early in life (Sullivan *et al.,* 2016).

Among the first bacterial species to appear 24 hours postpartum are *Staphylococcus spp., Streptococcus spp.,* and *neisseria spp*. Within the first 2 months of life the microbiome gradually diversifies and matures to a profile comparable to that of adults. Immediately following the peak of diversity and maturity, a readjustment occurs, where *Staphylococcus spp*. decline as early as 7 weeks postpartum, and is then replaced by an abundance in Streptococcus spp., among other bacterial species (Pattaroni *et al.,* 2018).

Neonatal microbial profile is influenced by the mode of delivery at birth; whether normal labor or caesarian section, and antibiotic misuse or abuse. Antibiotic-driven microbiome dysbiosis is associated with an increase in asthma burden in children (Patrick *et al.,* 2020).

Antibiotics, disturb lung homeostasis by acting directly on commensal bacteria, and also compromise the ability of the immunesystem to distinguish between self and non-self-antigen (Wypych and Marsland, 2018).

When antibiotics are administered, they can, non-selectively, remove the essential commensal bacteria that trigger the regulatory immune cells; hence the host will be susceptible to allergic disease development. Several studies have correlated asthma development to early-life antibiotic exposure (Ahmadizar *et al.,* 2017; Wypych and Marsland,

2018; Taylor *et al.*, 2018, Ni *et al.*, 2019). Typical and atypical bacterial respiratory colonization or infections may predispose to asthma or trigger asthmatic attacks and exacerbations. Bacterial microbiome composition and colonization during infancy plays a significant role as a determinant of respiratory health and potential asthma development.

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How to cite this article:

Gihan A. ELBatouti. 2022. Bacterial Pathogens and Bronchial Asthma: A Review. *Int.J.Curr.Microbiol.App.Sci.* 11(06): 1-9. doi: https://doi.org/10.20546/ijcmas.2022.1106.001