The Role of Chlamydia Pneumoniae in Asthma

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ABSTRACT

In asthmatic patients, the airway is very sensitive towards exogenous stimuli, a condition known as bronchial hyperreactivity. The definite causative agent for asthma is not known yet, so as bronchial hyperreactivity. Recently it was postulated that there was a role for infection of Chlamydia pneumoniae *in the pathogenesis of asthma. This paper will discuss about* Chlamydia pneumoniae *and its role in asthma, as well as its treatment.*

***Key words** : Chlamydia pneumoniae, Asthma*

INTRODUCTION

The word "asthma" originates from the Greek word meaning "difficulty breathing". Even though this illness has been introduced by Hippocrates over 2000 years ago, it remains a health problem.[1]

This disorder is found in every nation, and it turns out that out of all children with asthma, only 20% show absolutely no symptom of asthma at adulthood, while the rest demonstrate continuous, yet mild, wheezing. This means that most everyday asthma is chronic.[1, 2]

Even though many studies have been conducted, the definite causative agent for asthma is still unclear. This illness is also characterized by various etiology, pathogenesis, precipitant factors, severity of illness, and response towards therapy among those who suffer from it. The illness can even change in character from day to day, month to month, and year to year, [3] within a single patient.[1]

It has been known that the airways of asthmatic patients are overly sensitive to exogenous stimuli, a condition known as bronchial hyperreactivity (BRH). As with asthma, the definite causative agent for BRH is still unknown. In the year 1980, a close correlation between BRH and the inflammatory process was found. In allergic and non-allergic asthma, the inflammatory process demonstrates similar findings.[4]

In a workshop held by the National Institute of Health, National Lung and Blood Institute of the United States and the World Health Organization in March of 1996, a description of asthma was defined based on clinical, pathologic, and functional findings, as follows: Asthma is a chronic inflammatory disorder of the airway. Many cells are involved in this inflammatory process, such as mast cells, eosinophiles, and T lymphocytes.[5] Normal individuals are differentiated with asthmatics by oversensitivity. Allergens, work environment, cigarette smoke, and emotional stressors which do not induce asthmatic symptoms can induce asthma in an asthmatic.

The correlation between infection and asthmatic attacks has been known for long. A number evidence demonstrates that asthmatic attacks are induced by viral infection of the respiratory tract. A virus that has been greatly known to induce asthma is the Respiratory Synctytial Virus (RSV) in 50% cases, the Para Influenza virus in 20%, and Adenovirus in 13%. Infection usually occurs in children below two years of age. Blasi (1996) stated that intracellular bacterial infection such as Chlamydia pneumoniae plays a role in the development of asthma.[Quoted from 1]

CHLAMYDIA PNEUMONIAE

The Chlamydia genus includes the Chlamydiaceae family, consisting of three species, *C. psittaci*, *C. trachomatis*, and *C. pneumoniae*. It is a negative gram staining and intracellular obligate microbe.[6]

C. pneumoniae, also called Chlamydia TWAR, has gained attention as a case of respiratory tract infection.6 Almirall et al, conducted a study on the causative agents

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of 39,733 pneumonia cases in patients over 13 years of age.[7] *C. pneumoniae* turned out as the most common cause, followed by Streptococcus pneumoniae. In Japan, Niki (1995) reported *C. pneumoniae* as the cause of upper respiratory tract infection and acute bronchitis in 6.8% cases, pneumonia in 8.1% cases, acute exacerbation of chronic respiratory tract disease in 4.7% cases.[8]

Microbiological examinations for the detection of *C. pneumoniae* are culture, antigen detection, serological examination, and DNA (Deoxyribose Nucleic Acid) detection using PCR (Polymerase Chain Reaction). DNA detection using PCR demonstrated a sensitivity rate of 74.2% and a specificity of 96%. Such high sensitivity and specificity makes it a rapid and specific method of evaluation to diagnose *C. pneumoniae*.[9]

In Indonesia, up to now, infectious diseases are still the main cause of concern, one of which is respiratory tract infection. The problem of respiratory tract infection is not only found in Indonesia, but also almost all over the world. It is estimated that there are 2.2 million deaths due to respiratory tract infections. Research shows that causative microorganisms of respiratory tract infection may be bacteria, fungi, virus, or parasite. In the past, causative bacteria are limited to *Streptococcus pneumoniae*, *Haemophilus influenza*, *Staphylococcus aureus*, *Klebsiella pneumoniae*. Recently, there has been a major change in the causative agent, with the appearance of the new intracellular pathogenic bacteria, including *C. pneumoniae*.[Quoted from 10]

There are still no reports on microbiological findings of *C. pneumoniae* infection in Indonesia. This is because the diagnostic procedure uses Hela cell or egg yolk tissue culture, which requires a special, and very costly, laboratory. The same reason applies to detection using PCR.

In Jakarta, serological studies using the ELISA method has been conducted on 55 cases of lower respiratory tract infection, yielding 80% of cases with *C. pneumoniae*.[Quoted from 10]

We already know about the relationship between Helicobacter pylori and peptic ulcer. Several hypotheses have followed on the possibility of other pathogens involved in other acute and chronic gastrointestinal, neurological, cardiovascular diseases. Several clinical and epidemiological studies suspect a correlation between *C. pneumoniae* with respiratory tract and cardiac diseases.[11]

IMMUNITY

There are two different patterns in the seorological response towards *C. pneumoniae* infection. Microimmunofluorescence (MIF) examination found increased IgM titer, followed by IgG titer in primary infection. Re-infection turned out to increase titers of IgG and IgA, unaccompanied by IgM titer.

IgM antibodies usually can no longer be detected 2 to 3 months after acute infection, while IgG and IgA resides for a longer period of time. Such finding indirectly demonstrates persistent/chronic infection. Re-infection offer occurs, and no protective antibody appears.[6]

MIF is the gold standard for the detection of *C. pneumoniae* infection. This test has a higher specificity and sensitivity compared to culture and can determine Ig G, IgM, and Ig A (Blasi F, 1996) as in the table below.[12]

Table 1. Serologic Testing for the Detection of *C. pneumoniae*

MIF	Complement fixation
Acute infection Titers of Ig G or Ig A increased 4 folds, or: • Ig M ≥ 1:16 • Ig G ≥ 1:572 • Ig A ≥ 1:256 Recurrent infection • Ig G ≥ 1:16 ≤ 1:572 • Ig A ≥ 1:16 ≤ 1:256	Acute infection Titer increased 4 folds Titer ≥ 1:64

Quoted from 12

THE ROLE OF C. PNEUMONIAE IN ASTHMA

Hahn (1996) stated a hypothesis that *C. pneumoniae* is an intracellular non-viral microorganism involved in the:

1. Initiation
2. Exacerbation, and
3. Promotion of asthma.[13]

1. Initiation

Freyden et al (1989) was the first author to report cases of acute *C. pneumoniae* infection that could cause asthmatic bronchitis.[Quoted from 13]

Hahn DL et al (1991,1994),14,15 found that based on the study they conducted on 365 patients with acute respiratory tract infection, 19 (5%) suffered from acute infection based on serology, and 9 (47%) patients with *C. pneumoniae* infection demonstrated bronchial spasm, four with exacerbation of previously diagnosed asthma, and four were diagnosed with asthma for the first time.

It was then reported from further studies that 2 (40%) out of 5 new asthmatic patients were serologically found with *C. pneumoniae* infection.

Based on these findings, researchers suspect that acute *C. pneumoniae* infection plays a role as an initiator for asthma.

Emre et al (1994), 16 and Hahn DL (1995) later on reported the isolation of *C. pneumoniae* from culture, thus at the same time, asthma was initially diagnosed in one child and two adults. Another researcher, Thorn et al (1994), found an adult with hyperreactivity of the respiratory tract after infection of *C. pneumoniae* found from PCR examination.[Quoted from 13]

Larsen et al (1998), 17 and Cook PJ et al (1998), 18 based on the study they conducted, supported the opinion that *C. pneumonia* may act as an asthma initiator.

Hahn DL and MC Donald R (1998), 19 then recommended that chronic asthmatics be evaluated for the possibility of *C. pneumoniae* infection.

2. Exacerbation

Exacerbation of asthma is often related to respiratory tract infection. There have been many studies that found clear clinical and epidemiological evidence on the role of infection in acute exacerbation of asthma in children and adults. There has been difficulty in finding the causative microorganism, such as *C. pneumoniae*. [Quoted from 13]

Thorn et al (1994), 20 reported 19% out of 21 patients with acute respiratory tract infection due to *C. pneumoniae* who suffered from wheezing. In the same year, Allegra, et al, 21 also studied 74 adult asthmatic patients with exacerbation, and found serologic evidence of acute infection by *C. pneumoniae* in 7 (9%), by virus in 8 (11%), and by *Mycoplasma pneumoniae* in 1 (1%). *C. pneumoniae* has also been found in two patients of asthma exacerbation from the examination of throat swap under indirect immunofluorescence.

Other studies that supported the hypothesis that *C. pneumoniae* can induce the exacerbation of asthma have been conducted by Crayston YT (1994), 22 and Myashita et al (1998).23 Crayston has been even more assertive by entering *C. pneumoniae* in the list of agents capable of inducing acute asthmatic exacerbation.

3. Promotion

Hahn (1996), quoted from 13 mentioned that the hypothesis of chronic inflammation due to *C. pneumoniae* in asthmatic patient can be maintained if these three conditions are met:

a. The microorganism resides at the site of inflammation.
b. The immunopathological mechanism that induces inflammation in asthmatic symptoms should be known.
c. Treatment using antimicrobial agents and immunization improves asthmatic symptoms.

PERSISTENCE

A microbe is considered as a promoter of asthma if the microbe causes persistent infection and inflammatory destruction of the respiratory tract, thus causing asthmatic symptoms.

In the case of *C. pneumoniae*, this microbe has been proven to cause persistent infection in laboratory animals as well as humans, including asthmatic patients. Several markers of chronic infection include Ig A antibodies, proven by several studies (Hahn et al 1995, Hahn and Mc Donald 1995). [24,25]

IMMUNOPATHOLOGY

Busse (1993), 26 mentioned a possible immunopathological mechanism for *C. pneumoniae* to induce asthma through formation of Ig E, through mediator influence and destruction of respiratory tract epithelial cells, such as virus in asthma.

1. IgE specific

Hahn (1996) mentioned that Emre et al found IgE-specific organisms in 86% of positive culture findings in asthmatic patients with wheezing, and 9.1% positive culture in patients with pneumoniae unaccompanied by asthma, 22.2% negative culture in asymptomatic patients, and 9.1% negative culture in asthmatic patients.

2. Cytokines

C. pneumoniae has the ability to self-replicate within the lung macrophage, and can produce mediators such as tumor necrosis factor – alpha (TNF á), interleukin – 1 â (IL-1â), and interleukin – 6 (IL-6). Asthmatic symptoms have been proven to be correlated to TNF á, and IL-6 expression in the cells of the respiratory tract of asthmatic patients has been reported.

3. Epithelial destruction

Bronchoscopic examination on asthmatic patients demonstrates peeling of respiratory tract epithels and loss of cilliary cells. This results in increased BHR. Based on in vivo studies, *C. pneumoniae* were found to cause

cilliostasis of cilliary epithelial cells of the respiratory tract, as an initiation and pathogenesis of respiratory tract infection due to *C. pneumoniae*.

4. Influence on Alveolar Macrophage Function

C. pneumoniae infection causes malfunction of alveolar macrophage function, which could cause inflammation of the respiratory tract. In addition, destruction of macrophage may cause disturbance of the IgE mediated allergic inhibitory response towards inhaled allergens. Macrophage has also been demonstrated to play an important role in modulation immune response by preventing the function of sensitized T cells.

5. Heat Shock Proteins

Heat shock proteins (HSPs) are a collection of proteins involved in asthma. HSP may be related to inflammation of the respiratory tract of asthmatic patients.

TREATMENT

We then come to the question of the influence of antibiotic treatment on asthmatic patients accompanied by *C. pneumoniae* infection. To answer this question, we can see the results of the following two studies that hypothesized that antibiotic treatment on *C. pneumoniae* can improve asthma in the long term, even to the point of complete remission.

The first study was conducted by Emre et al (1994), 16 which performed treatment on 12 children with asthma accompanied by positive culture for *C. pneumoniae*. Administration of macrolide turned out to eradicate the microbe in all patients, and 9 (75%) demonstrated clinical and laboratory improvements of asthma.

The second study was conducted by Hahn (1994) 27 on 46 adult patients with chronic asthma and serologic findings of *C. pneumoniae*, with a mean age of 48 years. Complete remission was achieved in 7 patients, and clinical improvements in 18 patients. The average change in FEV_1 was 12%.

CONCLUSION

1. The incidence and mortality rate for asthma is quite high, including in Indonesia.
2. *C. pneumoniae* is an intracellular microbe that could cause respiratory tract infection, as well as play a role in asthma, as an initiator, exacerbation inducer, as well as a promoter.
3. *C. pneumoniae* is also found in Indonesia.
4. We hope to achieve more promising results in the treatment of asthmatic patients now and in the future.

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