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# Role of *Chlamydia pneumoniae* as an Inducer of Asthma

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## 1. INTRODUCTION

### 1.1. Definition of Induction

*Chlamydia pneumoniae* (Cpn) could have three distinguishable causal effects as an asthma inducer. First, an acute infection (or reactivation of a latent infection) could cause an acute worsening of preexisting asthma. Indeed, it is generally accepted that acute Cpn infection can cause some acute asthma *exacerbations*[1,2] but most evidence suggests that other organisms [mainly respiratory viruses, and, to a lesser extent, *Mycoplasma pneumoniae* (Mpn[3])] are associated with the majority of asthma exacerbations in both children[4] and adults.[5] Second, because of its propensity to produce persistent infection, Cpn chronic lung infection could cause worsening of established asthma over time. Again, Cpn has been associated with asthma severity[6] and a possible *promoting* role for Cpn in asthma is a focus of active investigation.[7] Third, an acute primary or secondary Cpn infection, in a previously asymptomatic nonasthmatic individual, could cause acute wheezing that develops into chronic asthma. That Cpn can *initiate* asthma is a radical idea for which there is some evidence[8] but how important a role Cpn plays as an asthma initiator remains to be determined. It is conceivable that acute Cpn infection, as an asthma initiator, could contribute to a substantial number of cases. This chapter focuses on the substantial body of evidence favoring a promoting role for Cpn, and also reviews the existing evidence for Cpn as an asthma initiator.

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## 1.2. Definition of Asthma

Asthma can be defined either by diagnostic or functional criteria. This distinction is important. In the United States, clinicians try to make clear-cut diagnostic distinctions between asthma, chronic bronchitis, and emphysema whereas in European countries, particularly the Netherlands, the tendency is to view these diseases as a continuum. This debate between "splitters"[9] and "lumpers"[10] has not been resolved to everyone's satisfaction. American asthma specialists have tended to view asthma as a noninfectious allergic (atopic) condition beginning in childhood and also have tended to diagnose older patients with asthma symptoms as chronic obstructive pulmonary disease (COPD), particularly if a history of smoking was present.[11] It is now apparent from population-based epidemiological studies that (1) neither atopy[12] nor allergen exposure[13] are primary causes for childhood asthma, (2) half of asthma may be related to nonatopic (neutrophilic) rather than to atopic (eosinophilic) inflammation,[14,15] and (3) adult-onset asthma (AOA) is as frequent as childhood-onset asthma.[16] Of further interest are data showing that smoking is associated with Cpn infection as well as COPD.[17,18]

The natural history of obstructive airways syndromes may evolve over a lifetime,[19,20] airway-disease-related variables (age, sex, smoking, pulmonary function, and markers for atopy) have unimodal and continuous distributions across clinical diagnoses,[21] and a significant minority of patients with asthma-like symptoms cannot be placed in the classical diagnostic categories.[10,21] To avoid diagnostic bias, it is probably more scientifically accurate to view atopy and smoking, along with other factors associated with asthma (e.g. bronchial hyper responsiveness), as covariates rather than as diagnostic attributes. For purposes of population-based, patient-outcome-oriented primary care clinical research, I favor the use of a functional definition for asthma based solely on cardinal symptoms (cough, wheeze, chest tightness, shortness of breath) and objective evidence for reversible airways obstruction determined by lung function testing.

*Persistent symptomatic reversible airway obstruction* is a common entity encountered in primary care settings.[16,21] The majority of cases are diagnosed as asthma, but the "overlap" syndromes [chronic asthmatic bronchitis and asthma with chronic airways obstruction (AS-CAO[22])] are often difficult to distinguish from asthma in clinical practice, respond to similar treatments, are linked to asthma in epidemiological studies and may represent later stages in the natural history of reversible airway obstruction.[10,19,22] The concept that asthma and COPD might have a common underlying etiopathology characterized by a unique host response to exogenous stimuli was proposed by Orie[23] and has become known as the "Dutch Hypothesis." The Dutch refer to obstructive airways syndromes (asthma and COPD) as *chronic nonspecific lung disease* (CNSLD),[10] and chronic Cpn infection has been proposed as an etiologic factor in CNSLD.[20] As well as reviewing the evidence for a role in the initiation and promotion of asthma, this chapter also reviews the evidence suggesting a role for Cpn in the development of lung remodeling, a cardinal feature of COPD.

### 1.3. Importance of Asthma

Asthma is an important cause of respiratory morbidity (symptoms, impaired quality of life, medication side effects), health care utilization (clinic and emergency room visits, hospitalizations, medication costs), and mortality. National costs for asthma in the USA were over $6 billion in 1990[24] and are steadily increasing since asthma prevalence leaped almost 20%, from 10.4 million to 12.4 million, between 1990 and 1992[25,26] and continues to rise. The history of an "infectious initiation"[27] and markers for chlamydial infection[28] may be significant risk factors for the development of COPD from nonatopic AOA. If COPD sequelae are included in the equation, costs of asthma are much greater than currently reported, since more than 16 million adults have COPD, and COPD accounts for approximately 110,000 deaths per year, $18 billion in direct health care costs and almost $10 billion in indirect costs.[29,30]

The incidence of asthma is greatest in childhood but the prevalence of active asthma is equally distributed between children and adults because of the longer period of time available for accrual of new cases of adult asthma[31] and the greater likelihood for asthma remission to occur in childhood-onset compared to AOA.[32] These facts account for the data that, nationally, patients 18 years or older account for 72% of direct costs, 61% of indirect costs, and 66% of overall costs of asthma care, excluding medications.[24] In one clinical setting, adults 19 years or older accounted for 51% of the costs of asthma treatment, including medications.[33] Death from asthma is a rare event in children, but asthma mortality increases steadily with age such that the mortality rate in the elderly population (age 70 and older) can be more than 40 times the death rate in children aged 14 or less.[34] It has been hypothesized that this age-related asthma mortality is due to the premature development of fixed obstruction known to accompany long-standing asthma.[35] These utilization data correlate with the clinical picture of asthma derived from numerous observations: compared with childhood-onset asthma, adult-onset asthma is associated with fewer markers of atopy,[36] more likely to affect women,[37] more clinically severe,[38,39] less likely to remit,[40,41] and associated with more fixed obstruction.[22,42,43]

### 1.4. Current Asthma Treatments Are Palliative, Not Curative

Current asthma treatment is based on a paradigm of asthma as a noninfectious atopic condition whose "root cause" is inflammation.[44,45] It is now well established that chronically administered antiinflammatory medications, primarily inhaled corticosteroids (ICS), ameliorate asthma symptoms and improve prebronchodilator $FEV_1$ (forced expiratory volume in 1 s).[46–49] However, the therapeutic effects of ICS treatment are not maintained upon discontinuation,[47] implying that ICS treatment is for the most part suppressive (palliative), not curative. The hoped-for additional effect that ICS treatment prevents the accelerated development of fixed obstruction in childhood asthma is not supported by evidence.[50,51] A randomized controlled trial found that ICS administration failed to slow the decline of postbronchodilator $FEV_1$ in adult