ASTHMA EXACERBATIONS

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Asthma is the most common chronic respiratory disease, affecting up to 10% of adults and 30% of children in the Western world. It is a heterogeneous disease that ultimately leads to the clinical constellation of cough, wheeze, and shortness of breath. These symptoms are accompanied by an

influx of inflammatory cells (1). Asthma exacerbations are acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, and chest tightness—or some combination of these symptoms. The signs of asthma exacerbation include agitation, increased respiratory rate, increased pulse rate, and decreased lung function as measured by FEV_1, peak expiratory flow (PEF), Pa_{O_2}, Pa_{CO_2}, and arterial oxygen saturation (Sa_{O_2}). The use of accessory muscles and the inability to talk in sentences or even in phrases might or might not be present, depending on the severity of the exacerbation.

The severity of these symptoms and signs, along with the findings on functional lung assessment, are used to categorize asthma exacerbations as mild, moderate, severe, or life-threatening. The primary determinant of severity is percent predicted FEV_1 or PEF. The exacerbation severity determines treatment. Mild exacerbations can usually be managed at home, but more severe exacerbations might require treatment and monitoring in the ED or, in more serious cases, hospital admission.

Despite advances in asthma management, acute exacerbations continue to occur and impose considerable morbidity on patients and constitute a major burden on health care resources. The frequency with which acute exacerbations occur in asthmatic patients varies depending on the definition used for the exacerbation, the severity and degree of control of the underlying disease, and the source of the data (2). Asthmatic patients requiring an emergency department visit or hospitalization are at significantly increased risk of future exacerbations independent of demographic and clinical factors, asthma severity, and asthma control (3).

Origins of asthma exacerbations

Although much childhood and adult asthma is associated with atopy, the classic notion that the majority of exacerbations in atopic patients with asthma are related to allergen exposure with resultant inflammation has been challenged by a number of studies (4).

The availability of monitoring of airway inflammation through measuring cell counts in induced sputum has indicated significant heterogeneity and changing patterns of inflammation during exacerbations, as well as during periods of unstable or poorly controlled asthma (5,6).

Eosinophilic inflammation, which is generally highly responsive to corticosteroid therapy, is considered to be a hallmark feature of exacerbations associated with allergen exposure, whereas neutrophilic inflammation is more generally associated with infective exacerbations, whether viral or bacterial.

Viruses

Since the early 1970s, viral respiratory tract infections have been reported as triggers for exacerbations of asthma in both adults and children (7,8).

The development of highly sensitive and specific molecular diagnostic and detection techniques in the 1990s led to greatly improved detection of respiratory tract viruses and allowed clear demonstration of the important link between viral infections and asthma exacerbations. When RT-PCR is used to supplement or instead of conventional culture techniques, viruses have been found in approximately 80% of wheezing episodes in school-aged children and in approximately one half to three quarters of the acute wheezing episodes in adults. Of the respiratory tract viruses identified in these circumstances, rhinoviruses are most commonly found and are detected approximately 65% of the time (9,10). Rhinovirus, like most respiratory viruses, replicates primarily in airway epithelial cells (ECs). In addition, rhinovirus infection induces expression of ICAM-1(intercellular adhesion molecule-1) to further the availability of receptors for rhinovirus to bind to and infect the cell (11). The induction of gene expression in rhinovirus-infected ECs appears to involve a double-stranded RNA–mediated pathway, suggesting that active rhinovirus replication triggers production of cytokines and chemokines that are necessary for the

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recruitment of inflammatory cells as well as being part of the host antiviral response (12).

Infection induces inflammation, increasing levels of neutrophils, eosinophils, CD41 cells, CD81 cells, and mast cells through increased mRNA expression and translation of IL-6, IL-8, IL-16, eotaxin, IFN-g–induced protein 10 (IP-10), RANTES, and other proinflammatory cytokines (13).

For example, IL-16 is a powerful lymphocyte chemoattractant that also activates eosinophils and macrophages. IL-6 and IL-8 play important roles in neutrophil trafficking. RANTES is a chemoattractant for eosinophils and lymphocytes, and the release of these and other proinflammatory cytokines can lead to airway hyperresponsiveness, inflammation, and mucus secretion.

Virus-induced asthma exacerbations are chiefly characterized by neutrophilic inflammation.

Rhinoviral infection also leads to an early release of IP-10, a chemokine involved in T-cell recruitment and mast cell activation. Asthmatic subjects have increased levels of IP-10 in serum; levels correlate with airflow obstruction, and high IP-10 levels are associated with a reduced bronchodilator response to b_2-agonists (14). These virologist and clinical outcomes in asthmatic subjects were strongly related to deficient IFN-g and

responses to rhinoviruses and other viruses in a range of cells.

IFN-b production in response to rhino viral infection is known to be reduced in asthmatic bronchial epithelium ex vivo, and this impairs an infected cell's ability to undergo apoptosis, allowing increased viral replication. Further interferon deficiencies with viral infection have been documented, including a reduced IFN-a response in PBMCs from asthmatic subjects 8 and reduced type III, or IFN-l, responses in bronchial epithelial cells and airway macrophages ex vivo.

Allergen sensitization and exposure

Environmental allergens are important factors in many aspects of asthma. More than 80% of children with asthma are sensitized to environmental allergens (1). The ubiquity of allergens, together with the high rate of sensitization to allergens in asthma, suggests that allergens play a significant role in asthma exacerbation. Allergens represent a highly diverse collection of molecules that evoke an acute allergic response in sensitized individuals and, as a consequence of this response, cause respiratory symptoms to occur. It is also appreciated that prolonged exposure to aeroallergens can result in chronic airway inflammation via Th2 driven IgE mechanisms. Such an immunological
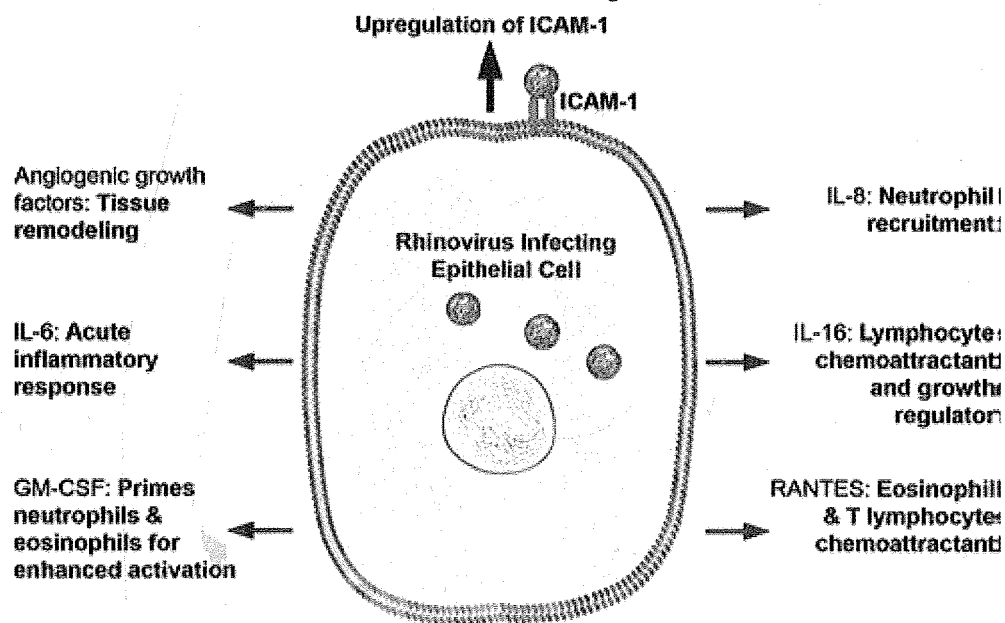
Figure nr.1 RV induces epithelial cells to produce proinflammatory cytokines leading to airway hyperresponsiveness, neurogenic inflammatory responses, mucous secretion, inflammatory cell recruitment and activation and plasma leakage.

IL-10 responses, and augmented IL-4, IL-5, and IL-13 responses (15).

So, the vulnerability of asthmatic subjects to rhinovirus might be due to a defect in interferon production. Interferons are antiviral proteins that have an important role in the innate response to infection, and asthmatic subjects have been shown to have deficient interferon

reaction may intensify airway inflammation, increase activation of inflammatory cells, and stimulate mucus glands to hypersecrete—all of which can cause airway obstruction.

Exposure to seasonal allergens has been implicated in sudden asthma-related deaths (16). Alternaria species

sensitization and exposure is associated with symptoms, (17) a 200-fold increased risk of respiratory arrest in asthmatic subjects, and house dust mite, cat, and cockroach sensitization are risk factors for emergency treatment. Grass pollen sensitization, or "thunderstorm asthma" has also been associated with epidemics of asthma exacerbations (18).

Thus allergen exposure is also clearly important in a number of acute exacerbations of asthma. A single study reported allergen-induced exacerbations were characterized by eosinophilic airways inflammation, (9) suggesting corticosteroids are likely to be the most effective current treatment for allergen-induced exacerbations; however, a synergistic interaction between allergen sensitization, allergen exposure, and viral infection has been detected in adult asthmatic subjects during acute exacerbations. Individuals who were sensitized, exposed, and infected had significantly increased risk of admission for exacerbations.

Bacterial infection

More than 40 years ago, Berkovitch et al (19) found evidence of infection with Mycoplasma pneumoniae in 18% of children with asthma exacerbations. Since then, numerous studies have investigated a possible association between bacteria (in particular the atypical organisms M pneumoniae and Chlamydophila pneumoniale) and asthma exacerbations. However, because many of the methods for detecting these organisms are not standardized, are insensitive, or are nonspecific, the results across in several other studies with rates of infection of less than 5%, highlighting the inconsistent nature of the association between atypical bacteria and asthma exacerbations.

While the clinical significance of M pneumoniae in asthma is under investigation, the mechanisms leading to asthma exacerbations are not well defined. In a murine model, acute Mycoplasma infection increased airway resistance with increases in both Th1 and Th2 cytokines (20).

Tumour necrosis factor (TNF)-a, IFN-c, IL-6, and IL-8 were all significantly increased in infected mice with airway features typical of asthma. In mice sensitized to ovalbumin, infection with Mycoplasma elicited a Th2 response; in animals not sensitized to ovalbumin, a higher induction of IFN-c occurred (21).

Therefore, in patients who have allergic sensitization and asthma, infection with Mycoplasma may serve to enhance existing allergic inflammation and thus provoke an exacerbation of the underlying chronic asthma.

Chlamydia pneumoniae impairs mucociliary clearance and increases mucus production in the lung. C pneumoniae induces cytokine secretion, including TNF-a, IL-1B, and IL-6, from PBMCs and alveolar macrophages.

In airway epithelial cells it also induces TNF-a, IL-8, IFN-g, and nuclear factor kB (NF-kB) with NF-kB activation, (22) and mouse models of Mycoplasma pneumoniae and C pneumonia infection cause airway hyper responsiveness and airway inflammation.

Further studies on the importance of atypical bacterial infections in acute exacerbations of asthma are clearly needed.

Current treatment guidelines indicate that antibiotics should not be given routinely in the treatment of acute exacerbations of asthma because evidence indicates viral infections to be the major cause. However, the evidence discussed above for a possible contributing role for atypical bacterial infection in acute exacerbations has prompted a recent study investigating the role of an antibiotic active against these infections.

A double-blind, placebo-controlled study randomized adults with asthma exacerbations to the ketolide antibiotic, telithromycin (a semi synthetic derivative of erythromycin) or placebo (31). The telithromycin group had significantly (approximately 2-fold) greater improvement in asthma symptoms and lung function from exacerbation to the end of treatment. Time to a 50% improvement in symptoms was also 3 days faster in the telithromycin group. This treatment effect might be the result of treating atypical infection, the anti-inflammatory properties of telithromycin, or both.

Macrolides can exert immunomodulatory properties separate from their antibiotic activity by inhibiting synthesis and secretion of proinflammatory cytokines, such as TNF-a, IL-8, and IL-6. Further studies are required to determine whether similar benefits are seen with related macrolide antibiotics.

Poorly controlled asthma

Severe or difficult-to-treat asthma, broadly defined as asthma that is refractory to treatment and poorly controlled over time, affects only 5% to 10% of the patient population, but it accounts for a disproportionate share of health care costs and morbidity associated with the disease (23).

The ability to identify patients at greatest risk for future severe exacerbation (FSE) is important for developing effective prevention strategies, reducing health care costs, and achieving the goals of asthma management (24).

A previous analysis of adult patient data from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study, the largest prospective, 3-year, multicenter observational study of patients with severe or difficult-to-treat asthma, showed that a recent severe exacerbation (RSE) or recent corticosteroid burst is a strong independent predictor of FSE (25). This was evidenced by significantly higher risks for the composite outcome of hospitalizations,

ED visits, or corticosteroid bursts in both children and adolescents/adults who had consistently VPC asthma compared with patients who improved from VPC asthma. These data support the 2007 asthma guidelines' impairment domain as a rigorous framework in which to classify a patient's asthma control and identify patients at risk for future asthma exacerbations. They also identified demographic and clinical factors predictive of consistently VPC asthma, specifically type of insurance, treating physician, lung function measures, and allergic triggers.

Although this study focused on applying the current asthma guidelines to predict future asthma exacerbations, other studies have approached prediction of exacerbations differently, including assessment of quality-of-life measures, psychometric tools, risk factors for hospitalization, and pharmacy data.

In a separate TENOR analysis involving patients aged 12 years or more, patients with a recent severe exacerbation (requiring an ED visit or night of hospitalization in the prior 3 months) were at a 3-fold greater risk of future exacerbation compared with patients without a recent severe exacerbation after adjusting for asthma control, 3 different guideline measures of severity, and demographic and clinical characteristics.

The TENOR Study Group demonstrated that adult asthmatic patients with 3 or 4 asthma control problems (barriers to optimal asthma management) were at significantly greater risk for unscheduled office visits, oral corticosteroid bursts, ED visits, or hospitalization (26).

Given the number and variety of studies that have been conducted, it is challenging to determine which measures or tools are best suited to evaluate risk for asthma exacerbations (27).

Bronchial thermoplasty

The most recent approach to the treatment of difficult-to-treat asthma is bronchial thermoplasty, which has been approved in some countries. This requires the patient to undergo fiberoptic bronchoscopy, and the central airways are treated with radiofrequency energy that is converted to heat ($65^\circ C$) in the airway wall. This heat ablates airway smooth muscle without causing any other damage to the airways (28). Initial studies of this treatment demonstrated clinical benefit in reducing symptoms and improving lung function and reducing mild asthma exacerbations (29).

A subsequent study has also demonstrated a significant reduction in severe asthma exacerbations (30). This treatment approach is associated with occasional need for hospitalization of patients after fiberoptic bronchoscopy, but long-term follow-up has not raised any safety concerns, and the clinical benefit appears to be maintained.

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