Asthma exacerbations – a review

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ABSTRACT
Exacerbation of asthma is a distinct clinical entity which results in a deterioration of asthma control sufficient to require medical intervention. Such exacerbations should be differentiated from poor asthma control due to inadequate anti-inflammatory or bronchodilator therapy. Asthma exacerbations adversely affect patient and family quality of life, result in time off work or school and cause significant costs to health care resources.

INTRODUCTION
One of the commonest reasons why patients present to primary care physicians and to emergency departments is because of an exacerbation of their asthma symptoms. Knowledge of the factors contributing to such exacerbations helps the physician to understand why these episodes occur, thereby enabling more effective work-up and management.

Various reasons why patients who are steroid-naive or well controlled on inhaled corticosteroids develop an exacerbation of their asthma symptoms include respiratory infections (viral, bacterial, atypical), allergens (aeroallergens, food additives and food allergens), exposures (occupational sensitizers, environmental, drugs), and miscellaneous factors (β-adrenergic receptor polymorphisms and non-respiratory factors) (Fig. 1). These trigger factors result in multicellular inflammation, bronchial hyperresponsiveness and airflow obstruction.

INFECTIONS
Viral infections
Viral infections of the respiratory tract are associated with 80-85% of asthma exacerbations with two-thirds of these infections being due to picornaviruses (mainly rhinoviruses). Coronavirus, the next most common virus, causes a less severe exacerbation while influenza, parainfluenza, adenovirus and respiratory syncytial virus occur in a proportion of patients. Human metapneumovirus (HMPV), a paramyxovirus closely related to respiratory syncytial virus (RSV) has been associated with acute wheezing exacerbations especially in infants and young children. Up to 12% of all lower respiratory tract infections may be due to HMPV in this age group. In South African children, the prevalence of HMPV was found to be 8.3% among those presenting with acute wheezing, while 7.4% were infected with human bocavirus and 2.4% with human coronavirus. In addition, viruses and Aeroallergens may have a synergistic effect on individuals with asthma, thus having a greater effect on the exacerbation rate together than either factor alone.

Respiratory syncytial virus
Respiratory syncytial virus (RSV) is an important cause of viral bronchiolitis in infants and young children, but their role in the pathogenesis of asthma and asthma exacerbations remains unclear. RSV infects almost 100% of children by 2 years of age. There are 2 subgroups of RSV-induced bronchiolitis, an eosinophil-positive group (with significantly raised eosinophil and interleukin-5 (IL-5) levels and raised IL-5/interferon (IFN)-γ ratios in bronchoalveolar lavage fluid) which results in a Th2 type response, and an eosinophil-negative group (with an absence of the Th2 cytokine profile). Since childhood asthma also induces a strong Th2 immune response, it is likely that infants with eosinophil-positive RSV-induced bronchiolitis, go on to develop childhood asthma. RSV is the predominant pathogen in wheezing infants younger than 2 years of age.

Rhinovirus
Rhinovirus (RV) is the most commonly recovered virus from the lower respiratory tract in acute exacerbations of asthma in children over the age of 2 years. It was previously thought that RV primarily caused an infection in the upper respiratory tract, but we now know...
that optimal replication of RV occurs between 33°C and 35°C, and thermal mapping of the airways in humans confirms that the temperatures found in the trachea and subsegmental bronchi will allow RV to replicate effectively in the lower respiratory epithelium. There are currently about 150 serotypes of RV and the majority (>90%) of the serotypes bind to intercellular adhesion molecule 1 (ICAM-1). The major human RV receptor is ICAM-1, and the gene for this receptor is located on chromosome 19. RV infection of the lower respiratory tract markedly increases cell surface expression of ICAM-1 in bronchial and respiratory epithelial cells by induction of ICAM-1, promoter activity involving upregulation of NF-κB, together with increasing ICAM-1 mRNA transcription. The net result is an increased RV infiltration of epithelial cells of the lower respiratory tract.

IFNs are antiviral proteins with an important role in the innate immune response to viral infections. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with RV in that they produce more than 2.5 times less IFN-β protein, and this impairs the infected cell's ability to undergo apoptosis, thereby allowing increased viral replication to occur. Patients with allergic asthma also produce significantly lower amounts of IFN-α following viral infections. Deficient induction of IFN-γ by RV in asthmatic bronchial epithelial cells has also been demonstrated. This paves the way for rhinoviral infection of the respiratory epithelial cells.

The next step is activation of the respiratory epithelial cells to produce pro-inflammatory mediators. RV infection results in an increased mRNA expression and translation of IL-6, IL-8, IL-16, eotaxin and RANTES (Regulated on Activation, Normal T cell Expressed and Secreted). IL-6 and IL-8 are pro-inflammatory cytokines. IL-8 is a potent chemoattractant for neutrophils. Neutrophils predominate more frequently than eosinophils as the major inflammatory cell in sputum from patients with asthma in acute exacerbations following viral infections. RANTES is a chemokine with chemoattractant activity for eosinophils, monocytes and T-lymphocytes. IL-16 activates eosinophils and is a chemoattractant for lymphocytes. Generation of these cytokines results in deterioration of lung function.

**Bacterial infections**

Clinical and experimental studies indicate that sinonasal inflammation can result in worsening of lower airways disease, induced by post-nasal drip, nasobronchial reflux of inflammatory mediators. Organisms which may be cultured in maxillary sinus aspirates include Moraxella catarrhalis, nontypeable Haemophilus influenzae and streptococcal pneumonia. Effective medical and surgical treatment of sinusitis may result in clinical improvement of the asthma symptoms. Furthermore, chronic sinusitis has been suggested as playing a causal role in difficult-to-control asthma.

Asthma is an independent risk factor for invasive pneumococcal disease. The respiratory airways of asthmatics display goblet cell hyperplasia, which results in increased production of mucus. Alterations in the secreted mucus results in abnormalities in viscosity and in the mucociliary clearance of the airways which can serve as a focus for localised infection that can develop into invasive bacterial infection.

**Atypical bacterial infections**

Mycoplasma pneumoniae and Chlamydia pneumoniae are significantly related to wheezing in children, especially in those with a history of recurrent episodes. This suggests a potential role for these pathogens in the exacerbation of childhood asthma. In children with wheezing, the incidence of M. pneumoniae and C. pneumoniae infections increases with age and occurs mainly after 5 years of age.

Telithromycin, a new ketolide antibiotic, as well as macrolide antibiotics, has shown benefit in adults with acute exacerbations of asthma. Although the exact mechanism of the benefit is unclear, the findings suggest that atypical bacterial infections may be related to acute asthma exacerbations. However, it needs to be remembered that the ketolide and macrolide antibiotics have also been shown to have immunomodulatory effects both in vitro and in vivo, on the migration of neutrophils and production of pro-inflammatory cytokines. Therefore, more research and understanding are needed to define the precise roles of atypical bacteria in asthma exacerbations and the anti-inflammatory role of ketolide and macrolide antibiotics in this condition. The anti-inflammatory properties these antibiotics are considered to possess may actually be a secondary effect to an antimicrobial action to as yet unidentified respiratory tract bacteria.

**ALLERGENS**

**Aeroallergens**

Epidemics of asthma exacerbations have been observed following thunderstorms, with the strongest association in late spring and summer. A marked increase in the ambient concentration of grass pollen grains has been implicated in this condition. Thunderstorms are also associated with increased levels of Alternaria and Cladosporium species and sensitisation to these moulds correlates with asthma exacerbations and hospitalisations.

Sensitisation to mites, cat and cockroach has been found to be a significant risk factor for worsening asthma symptoms. However, there is no clearly established quantitative relationship between current exposure to these perennial allergens and asthma exacerbations.

**Food additives and food allergens**

Sulphites are antioxidants that are used as preservatives in foods and drugs, especially in injected and inhaled medications, and as antimicrobial agents in wine. They are used on dehydrated vegetables, dried fruits and in fruit drinks. Sulphiting agents include sulphur dioxide, sodium sulphite, and potassium and sodium salts of bisulphite and metabisulphite. Exposure to sulphites in an asthmatic who is sensitive to these agents may result in significant bronchospasm. Although injectable adrenaline (Epi-pen) contains sodium metabisulphite as an antioxidant, it may still be safely used if a patient experiences a severe systemic reaction as a consequence of sulphite exposure.

Tartrazine, a synthetic yellow food dye has not been shown to cause asthma exacerbations, even among aspirin-sensitive asthmatics. Asthma alone is an infrequent manifestation of food allergy. The major foods incriminated in the production of asthma in children are milk, eggs, soy, wheat, peanut, fish, tree nuts and shellfish. Acute respiratory symptoms to these antigens are an IgE-mediated reaction. More often, there are associated cutaneous, gastrointestinal and cardiac symptoms resulting in anaphylaxis.

**EXPOSURES**

**Occupational sensitisers**

Occupational asthma (OA) refers to bronchial inflammation directly resulting from the inhalation of dusts,
gases, fumes or vapours at the workplace. This results in variable airflow obstruction and bronchial hyper-reactiveness, after a latent period of exposure to such agents.

Allergic OA is caused by high molecular weight (HMW) allergens and some low molecular weight (LMW) allergens. HMW allergens are mainly proteins derived from animals (e.g. animal protein in laboratory settings), plants (e.g. coffee bean dust in food processing), foods (e.g. flour in bakeries) and enzymes (e.g. protease and amylase in detergent manufacture). Sensitisation to these agents elicits a Th2 immune response with the production of specific IgE. Some LMW agents, such as antibiotics (e.g. penicillins in the pharmaceutical industry), metals (e.g. platinum salts, chrome and nickel in the metal-refining industry) or isocyanates (e.g. in the spraypainting industry) also elicit a Th2 immune response.

Non-allergic OA occurs as a result of high level exposure to potent respiratory irritants in the workplace. This results in non-immunological bronchial inflammation with resultant bronchoconstriction termed reactive airways dysfunction syndrome (RADS). Typically, there is a latent period prior to the presentation of bronchial symptoms. Industrial agents which are known to cause RADS include chloride, sulphuric acid and toluene disocyanate used in the production of polyurethane products.26

Environmental exposures

Exercise, cold air, environmental pollutants and tobacco smoke are recognisable factors associated with aggravation of asthma symptoms.

Exercise-induced asthma usually results in transient narrowing of the airways following the cessation of vigorous exercise. The ‘thermal hypothesis’ proposes that cooling of the airways is followed by rapid rewarming resulting in reactive hyperaemia of the bronchial micro-circulation and oedema of the airway wall, thus causing bronchoconstriction after exercise.27 Exercise-induced bronchospasm (EIB) phenotype is characterised by increased production of cysteinyl leukotrienes which may be mediated by sensory nerves. EIB may on occasion result in a severe bronchospasm and has been associated with sports-related deaths.

Cold air results in reflex bronchoconstriction and has been used as a diagnostic test for demonstrating bronchial hyperreactivity.

Outdoor air pollution results in increased risk for asthma exacerbations. Polluted air may contain a mixture of ozone, nitrogen dioxide, sulphur dioxide, lead, carbon monoxide and particulate matter. Vehicular exhaust emissions contain ultrafine particulate matter, carbon, nitrogen dioxide and carbon monoxide and even short-term exposure to such emissions is associated with neutrophilic inflammation of the airways.28

Tobacco smoke exposure has been associated with asthma exacerbations and has been identified as a significant risk factor for asthmatic children, requiring intubation.29 According to a recent Institute of Medicine report, smoking in the home is causally related to exacerbations of asthma in preschool-aged children.30 Various mechanisms result in a state of corticosteroid resistance in asthmatics who smoke. Furthermore, cigarette smoking causes a downregulation of the β-adrenergic receptor function which impairs the clinical response to β2-agonists, thus potentiating an exacerbation.31

Drugs

Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and β-blockers have been associated with asthma exacerbations. Aspirin-induced asthma is a clinical syndrome which involves intolerance to aspirin and other NSAIDs which inhibit cyclo-oxygenase. This results in alterations in arachidonic acid metabolism and an overproduction of leukotrienes resulting in asthmatic attacks when these drugs are ingested. Beta-blockers in general and non-selective β-blockers (e.g. propanol) in particular have the potential for worsening bronchospasm and inhibiting therapeutic responses to inhaled β-agonists.

MISCELLANEOUS

Beta-adrenergic receptor polymorphisms

Polymorphisms of the β2-adrenergic receptor can affect regulation of the receptor.32 Patients who are homozygous for arginine at codon 16 of the receptor (Arg/Arg) have worsening of their lung function with regular versus as-needed use of inhaled β2-adrenergic agonists. This effect is not observed in asthmatics homozygous for glycine (Gly/Gly) or in patients with the Arg/Gly genotype. The first prospective clinical trial, stratified by genotype, confirmed that genotype at the 16th amino-acid position of the β-adrenergic receptor affects the long-term response to albuterol use and suggested that bronchodilator treatments avoiding albuterol may be appropriate for patients with the Arg/Arg genotype.33

A similar result was demonstrated when long-acting β-agonists were studied. Relative to patients with the Gly/Gly genotype at position 16 of the β-adrenergic receptor, Arg/Arg genotype patients have an impaired therapeutic response to salmeterol in either the absence or presence of concurrent inhaled corticosteroid use.34

The prevalence of the Arg/Arg genotype in asthmatic patients in South Africa is unknown while a sixth of USA asthmatic patients have this genotype, and the frequency is even greater in individuals of African decent.35

Much debate has been initiated following the results of these trials with some researchers showing that response to salmeterol does not vary between β-adrenergic receptor genotypes after chronic dosing with an inhaled corticosteroid.35 Therefore, more research is needed in this area to clarify the relationship between β-adrenergic receptor genotypes and regular bronchodilator usage.

Non-respiratory factors

There is a strong association between gastro-oesophageal reflux, psychological dysfunctioning, obstructive sleep apnoea and recurrent exacerbations of asthma. Pathological gastro-oesophageal reflux is considered a potential trigger of asthma. Mechanisms of this acid-induced bronchoconstriction include a vagally mediated reflex and microaspiration. A subgroup of patients gains improved control of asthma with treatment of gastro-oesophageal reflux. Although psychological dysfunctioning has been strongly associated with recurrent asthma exacerbations, more studies are needed to clarify whether psychological disturbances are the cause or consequence of the loss of control in asthma. Snoring and obstructive apnoea may trigger nocturnal asthma attacks. In some unstable asthmatic patients, improvement in asthma control has occurred after nasal continuous positive airway pressure.36
CONCLUSION
In the majority of patients, asthma can be reasonably well controlled with inhaled anti-inflammatory drugs. A proportion of patients however suffer from frequent exacerbations of the condition, leading to emergency outpatient treatment or hospitalisation. Understanding the various factors affecting such exacerbations may result in improved management and prevention of such exacerbations.

Declaration of conflict of interest
The author declares no conflict of interest.

REFERENCES