

Medical algorithms: Approach to adult asthma exacerbations

An “operational” definition of an exacerbation of asthma is a (sub) acute worsening of asthma symptoms that requires a change in treatment. To standardize definitions for the purpose of clinical research and to categorize the severity, ERS and ATS jointly¹ proposed that severe exacerbations are those that require treatment with systemic corticosteroids for at least 3 days or a hospitalization or emergency room visit for asthma that requires systemic corticosteroids. Any worsening for at least 2 days, which requires additional treatment, but not systemic corticosteroids was considered moderate. These events may not necessarily be acute events, but rather could develop over 5–7 days. A mild exacerbation (a poorly defined state) may

involve only a transient loss of asthma control over 7–10 days. These definitions, while helpful, still are not specific for symptoms that may be due to airflow obstruction and do not account for the underlying pathobiological processes. For example, an infective bronchitis that results in airway neutrophilia and mucus necessitating treatment with antibiotics or mucus clearing strategies would not be considered an exacerbation. Likewise, the response to treatment, for example increasing the dose of inhaled or systemic corticosteroids, is not often ascertained. Therefore, multi-variate and modern real-time fluctuation analysis that incorporates symptoms, lung function and biomarkers may be helpful to define asthma exacerbations.²

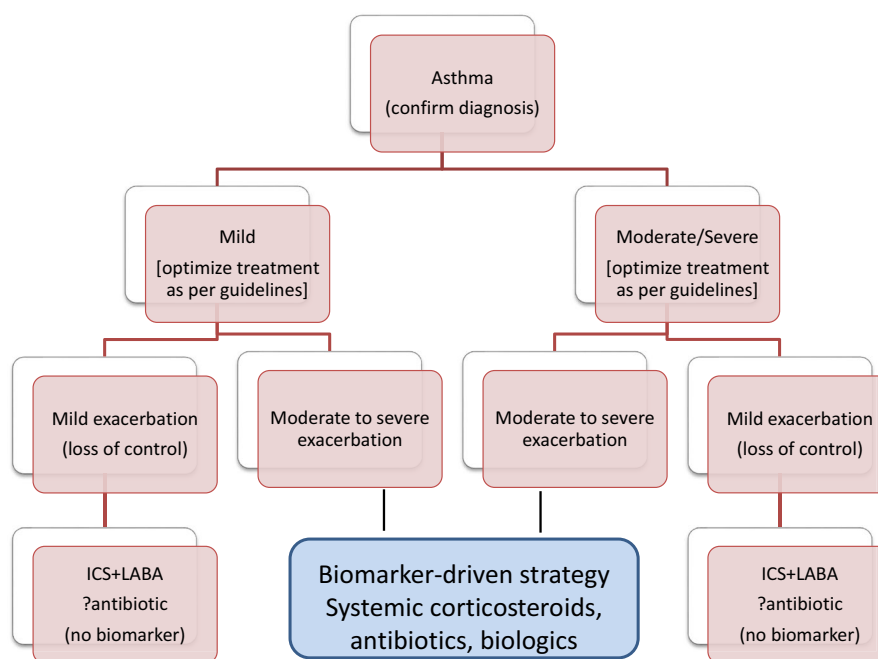


FIGURE 1 Algorithm to manage exacerbations. The first step would be to confirm that symptoms are indeed due to asthma (ie, variable airflow obstruction). After assessing level of control (based on symptoms), and severity (based on intensity of anti-inflammatory treatment and bronchodilators required to maintain control), treatment would depend on the severity of exacerbations, as recommended by international guidelines. While mild exacerbations (loss of asthma control) may be treated by escalating the dose of maintenance ICS and LABA, (or adding LAMA or SAMA) (and may not require any biomarkers), more severe exacerbations (independent of the severity of asthma) are probably best guided by biomarkers such as blood or sputum eosinophils and exhaled nitric oxide. In future, precision medicine is likely to evolve handprints of specific inflammatory pathways that might be targeted in individual patients. LABA, long-acting beta-adrenergic agonists; LAMA, long-acting muscarinic antagonist; SAMA, short-acting muscarinic antagonist

Despite the imprecision and variability of definitions, the consequences of these exacerbations are well recognized. The severity of exacerbations may not always relate to the severity of asthma that is usually defined based on the intensity of baseline therapy. Patients with mild asthma may develop a severe exacerbation (ranging from 0.2 to 2.9/patient/year),³ that may rarely even be fatal, and patients with severe asthma may have a mild or moderate exacerbation. Not only do the exacerbations have an immediate impact on morbidity and quality of life, but successive exacerbations may lead to progressive loss of lung function. It is now recognized that poor asthma control increases the future risk of exacerbation. Therefore, international guidelines emphasize not only appropriate treatment of the exacerbations, but to optimize baseline asthma treatment to improve asthma control to reduce future risk. This brief document suggests algorithms to prevent and treat exacerbations. It does not discuss management of acute severe asthma.

The cornerstone of asthma management is inhaled steroids even for the mildest of asthmatics. New evidence demonstrates that a combination of inhaled steroid and a long-acting beta-agonist with

a rapid onset of action used as reliever therapy would be a better choice for mild patients than a beta-agonist used on its own, both to improve baseline asthma control and to reduce risk of future exacerbations.⁴ This strategy may also reduce the risk of a mild exacerbation progressing to a severe exacerbation.⁵ Other important management strategies are to ensure compliance to treatment and adequacy of inhaler use, and to remove any identifiable exposure to sensitizers. Quadrupling the dose of maintenance treatment may be helpful in some patients. For many of these patients, additional biomarkers such as sputum eosinophil counts or fraction of exhaled nitric oxide, or composite markers⁶ are probably not necessary to achieve additional treatment benefits (Figure 1).

However, in patients with severe asthma, and in those with mild asthma who may have severe exacerbations, it would make intuitive sense to identify the components of asthma that may have contributed to asthma severity and the luminal obstruction associated with an exacerbation (Figure 2). This is particularly relevant to guide treatment with biologicals that are directed against the Th2 cytokines, and to identify exacerbations that are associated with

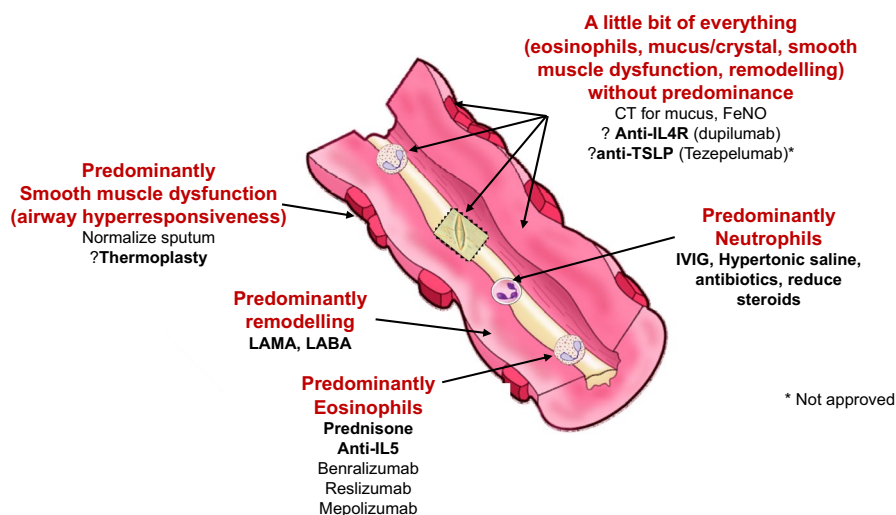


FIGURE 2 Choice of treatment of severe exacerbations guided by biomarkers and causes of luminal obstruction. Identification of the “dominant” contributor of symptoms and an individual exacerbation determines optimal treatment. These may be excessive smooth muscle constriction (or failure of relaxation), or luminal mucus, cells (mostly eosinophils or neutrophils), or crystals (eg, Charcot Leyden), or a combination of these. This could change over time in the same patient and therefore needs to be re-assessed at each exacerbation. Persistent and recurrent sputum eosinophilia (>3%, but usually over 20%) would suggest eosinophil as a key effector cell and therefore would predict the exacerbation to respond to corticosteroids or anti-IL-5 biologics. Persistent intense neutrophilia would prompt investigations for susceptibility to infections, that include CFTR gene abnormalities and immunodeficiencies, and treatment with appropriate antibiotics guided by extended culture and sensitivity studies. It is important to limit the use of corticosteroids in these patients. Some of these patients may respond to prolonged treatment with macrolide antibiotics (eg, azithromycin 250–500 mg on alternate days for 6–12 months, particularly if the cultures are negative or if the bacterium identified is consistently *Hemophilus influenzae*). Patients who have combined eosinophilic and neutrophilic exacerbations usually have the most severe outcomes and would require combination of anti-Th2 therapies and antibiotics, and further investigations as to underlying immunology. Paucigranulocytic sputum associated with severe airway hyperresponsiveness (methacholine PC₂₀ usually <0.5 mg/ml) may be associated with mast cell-mediated myositis or severe smooth muscle dysfunction and may respond to treatment with bronchial thermoplasty or small molecules directed against receptor tyrosine kinase (eg, masitinib, JAK inhibitors). These require further investigation. The precise role of anti-alarmins (eg, anti-TSLP, tezepelumab, and anti-IL-4R-directed therapies, dupilumab) is currently being evaluated. They may be effective in a broad range of immunopathologies, particularly associated with sinus disease, airway mucus or airway autoimmune features, without one dominant cause of luminal inflammation, as they have not yet been demonstrated to decrease luminal eosinophils in severe asthma. If sputum biomarkers are not available, decisions are likely to be less precise. A combination of raised blood eosinophil count (≥300 cells/μl) and fraction of exhaled nitric oxide ≥35 ppb is likely to indicate response to Th2 cytokine-directed therapies

bacterial infections. Biomarkers in blood, sputum, urine, and exhaled breath, ranging from simple enumeration of inflammatory cells to composite fingerprints of proteomic, transcriptomic and metabolomic data, are being evaluated to guide therapy. Exacerbations associated with significant sputum eosinophilia ($\geq 3\%$) and possibly blood eosinophilia (≥ 300 cells/ μL) (indicating Th2 immunobiology) respond well to increased inhaled or oral corticosteroids, while those with significant sputum neutrophils (total cell count >10 million cells/g and neutrophils $>65\%$) generally indicate bacterial infections that require treatment with antibiotics.

Recurrent neutrophilic exacerbations ought to prompt to examine reasons for susceptibility to airway infections.⁷ It is recommended that sputum be re-evaluated after 4–6 weeks after a treatment change. Eosinophilia that persists despite prednisone treatment usually indicates a residual Th2 inflammation largely mediated by IL-5 and IL-13, with contribution from alarmins such as IL-33 and TSLP. Monoclonal antibodies that target IgE (omalizumab), IL-5 (mepolizumab and reslizumab), the IL-5R (benralizumab), the IL-4R (dupilumab), and TSLP (tezepelumab) have reduced exacerbations while on high doses of corticosteroids.⁸ A scheme to guide therapy based on the dominant contributor of luminal obstruction and exacerbation as assessed by sputum examination is shown in Figure 2. It is advisable to assess airway secretions (sputum or bronchial wash) if a patient exacerbates while on an anti-IL-5 biologic before switching to an alternate biologic. This is because majority of exacerbations while on mepolizumab or reslizumab are likely to be eosinophilic (and therefore may respond to more prednisone, or by switching to benralizumab), while most exacerbations on benralizumab are likely to be non-eosinophilic and mostly neutrophilic due to bacterial infections.⁹ Blood eosinophil count may be normal in these patients. Since anti-IL-4R mab (dupilumab) is not demonstrated to decrease airway eosinophilia, exacerbations on dupilumab are also likely to be eosinophilic. Exacerbations associated with severe airway hyperresponsiveness and normal sputum cell counts may benefit from bronchial thermoplasty.

In summary, it is important to confirm the diagnosis of asthma (with objective evidence of variable airflow obstruction), and to assess the level of control and baseline severity, and to optimize treatment to prevent the risk of future exacerbations. Judicious use of inhaled steroids and long-acting beta-agonists guided by simple clinical assessments and spirometry would be effective to prevent most exacerbations in patients with mild-to-moderate asthma. In patients with severe asthma, or patients who have had severe exacerbations, biomarker-driven optimization of therapy leads to better outcomes. Assessment of airway luminal inflammation using sputum cytometry is recommended to assess exacerbations while on anti-Th2 biologics. Neutrophilic exacerbations usually indicate airway infections. Presently, we do not quite understand the reasons for exacerbations that do not seem to be associated with luminal inflammation. Targeting the airway smooth muscle, mucus or mast cells need further evaluation.

KEYWORDS

asthma treatment, biologics, biomarkers

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Parameswaran Nair 

Paul M. O'Byrne

Firestone Institute for Respiratory Health, St Joseph's
Healthcare & Department of Medicine, McMaster University,
Hamilton, ON, Canada

Correspondence

Parameswaran Nair, Firestone Institute for Respiratory
Health, St Joseph's Healthcare Hamilton, 50 Charlton
Avenue East, Hamilton, L8N 4A6 ON, Canada.
Email: parames@mcmaster.ca

ORCID

Parameswaran Nair  <https://orcid.org/0000-0002-1041-9492>

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