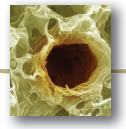

Management of Asthma in the Military

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This article examines the evaluation and management of asthma based on current guidelines, advances in therapy, and the challenges of managing asthma in today's military.

Asthma is a chronic inflammatory disorder of the airways that leads to airflow obstruction and bronchial hyperresponsiveness. Clinical features of asthma include episodic cough, wheeze, and dyspnea, which may resolve with avoidance of triggers or therapy. Characteristic triggers of asthma are irritant-type airway exposures, including cold air, exercise, various environmental allergens, and work-related exposures. Work-related exposures are the etiology for occupational asthma and work-exacerbated asthma, accounting for up to 25% of adult-onset asthma.[1] It is imperative that clinicians evaluate the clinical history, pulmonary function testing, and response to prior therapies when caring for patients with asthma.

Asthma is common in active-duty service members, despite the diagnosis limiting entrance into the military, and there is potential for significant rates of underdiagnosis among new recruits.[2] Recent changes in military medical guidelines have allowed service members with well controlled asthma to remain on active duty.[3] This potentially increases the number of service members with compromised respiratory status, which is concerning in light of the past decade of deployment to southwest Asia (SWA) and ongoing investigations into potential deployment-related irritant respiratory exposures.

DIAGNOSIS

An accurate initial diagnosis is a critical starting point in the management of asthma. Many diseases can mimic asthma, including vocal cord dysfunction, chronic obstructive pulmonary disease (COPD), congestive heart failure, sarcoidosis, allergic bronchopulmonary aspergillosis (ABPA), and eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome (Table 1).[4] Asthma-mimics, in particular ABPA and EGPA, are often diagnosed via careful longitudinal follow-up.

Characteristic symptoms of asthma include cough, wheeze, dyspnea, chest tightness, and sputum production. Symptoms should be described systematically in terms of onset, frequency, duration, diurnal variability, and seasonality. A careful review of systems should be conducted to exclude conditions such as COPD, pulmonary emboli, congestive heart failure, viral syndromes, acute infection, or hypersensitivity pneumonitis. Patients must be queried (carefully and often repeatedly) about potential triggers, including physical activity, hobbies, pets (including any animals owned by the patient, family members, or living on the property), and occupation.

Physical examination may reveal presence of nasal polyps, nasal mucosal swelling, increased secretions, wheezing, a prolonged expiratory phase, atopic dermatitis, or eczema. Further cardiac evaluation with transthoracic echocardiography may be considered in patients with a heart murmur. Digital clubbing is not characteristic of asthma and should prompt investigation of alternative inflammatory disease (connective tissue disease, interstitial lung disease, or bronchiectasis).

Pulmonary function testing including spirometry and bronchodilator response should be performed as demonstration of airflow limitation is crucial for the diagnosis of asthma.[4] Spirometry should be performed in accordance with published standards and documented in the patient's medical record. Airflow limitation should be

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Table 1. Differential Diagnosis in Adults With Suspected Asthma

Diagnosis	Symptoms	Testing
COPD	Smoking history Aged > 35 years Chronic cough	Hyperinflation and flattened diaphragms on CXR Emphysema and air-trapping on CT Fixed obstruction on spirometry
Allergic rhinitis	Rhinorrhea Nasal obstruction	Empiric therapy with: Nasal corticosteroids Antihistamines Allergy testing
GERD[a]	Acid reflux	pH probe Empiric therapy with PPI
Coronary artery disease Congestive heart failure	Orthopnea Paroxysmal nocturnal dyspnea Peripheral edema	Elevated pro-BNP Cardiomegaly and reduced LVEF on TTE
Vocal cord dysfunction	Inspiratory wheeze or stridor	Inspiratory symptoms Spirometry may have truncated inspiratory loop Laryngoscopy with inspiratory vocal cord closure
Allergic bronchopulmonary aspergillosis	Wheezing Fatigue Fever Brownish sputum	Elevated serum eosinophils and IgE Serum precipitins to aspergillus Obstructive spirometry Bronchiectasis Migratory infiltrates
Churg-Strauss syndrome or eosinophilic granulomatosis with polyangiitis	Long-term multiphase disease Multi-organ involvement	Elevated serum eosinophils IgE and ANCA positivity
Sarcoidosis	Dyspnea Wheezing Cough	Noncaseating granulomas
Bronchiectasis	Productive cough Wheezing	Airway enlargement Localized infiltrates Mild obstruction
Pulmonary embolism	Chest pain Sinus tachycardia Risk factors for VTE	Hypoxemia Elevated D-dimer CT chest with PE protocol
Cystic fibrosis	Productive cough Recurrent sinopulmonary infections	Abnormal sweat chloride test Hyperinflation Bronchiectasis

Abbreviations: ANCA, anti-neutrophil cytoplasmic antibody testing; COPD, chronic obstructive pulmonary disease; CT, computed tomography; CXR, chest plain film radiography; GERD, gastroesophageal reflux disease; IgE, immunoglobulin E; LVEF, left ventricular ejection fraction; PE, pulmonary embolism; PPI, proton pump inhibitor; pro-BNP, brain-natriuretic peptide; TTE, transthoracic echocardiography; VTE, venous thromboembolism.
[a]Typical symptoms may be absent in some patients with GERD, and the diagnosis may require a high-index of suspicion.

described in accordance with the Third National Health and Nutrition Examination Survey (NHANES III) references values as recommended by the American Thoracic Society and the European Respiratory Society (ATS/ERS) guidelines.[5-7] Obstruction is defined as an forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) ratio less than the fifth percentile of the normal distribution (lower limit of normal). Bronchodilator testing should also be performed to establish presence and degree of response to inhaled

Table 2. Classification of Asthma Severity[9]

Exacerbations	Intermittent	Mild	Moderate	Severe
Symptoms	> 2 d/wk	> 2d/wk but < 1/d	Daily	> 1 daily
Nighttime awakenings	< 2x/m	> 2x/m	> 1/wk	Nightly
Use of short-acting beta-agonists	< 3 d/wk	≥ 3 d/wk	Daily	Several times daily
Interference with activity	None	Minor limitation	Some limitation	Extremely limited
FEV_1	> 80% predicted	> 80% predicted	60%-80% predicted	< 60% predicted
FEV_1/FVC ratio	Normal	Normal	Decreased	Decreased
Risk	< 2/y	≥ 2 Exacerbations/y requiring oral or parenteral steroids		

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

bronchodilator medication. A12% increase in the FEV_1 with an absolute increase of 200 mL is considered significant in adults.[7]

It is important to note that although a positive bronchodilator response is highly suggestive of asthma in the appropriate clinical circumstance, it is not required for diagnosis, and inhaled bronchodilators may be useful in disease management even in the absence of a positive response. Patients with nonspecific reductions in the FVC, with symptoms not consistent with asthma, or not responding to typical asthma therapy are more likely to have been falsely diagnosed. These patients should have lung volumes and diffusion capacity of carbon monoxide measured to evaluate for other potential etiologies (eg, parenchymal lung disease, pulmonary vascular disease).[4]

Bronchoprovocation testing is useful for demonstrating airway hyperresponsiveness in a patient with symptoms suggestive of asthma, particularly those with normal baseline spirometry. Patients should have testing performed and interpreted in accordance with ATS standards.[8] Although methacholine challenge testing is preferred, other methods including cold air or eucapnic hyperventilation are also established. Exercise challenge testing, although less sensitive, remains a useful tool, particularly in patients with primarily exertional symptoms. It is important to note that a positive bronchoprovocation test result may occur in other conditions. Whereas a positive test is consistent with asthma, a negative test may be more useful to exclude the diagnosis.[8]

Finally, chest imaging with plain film radiographs (posteroanterior and lateral views) is important to exclude parenchymal lung disease or mediastinal disorders. Further imaging with computed tomography is not indicated in the absence of atypical clinical features (such as abnormal plain films or failure to respond to therapy).

MANAGEMENT

The initial management of asthma in based on severity and follows a stepwise progression according to the 2007 National Asthma Education and Prevention Program.[9] Severity is determined by the following factors: symptoms in the past 2 to 4 weeks, pulmonary function testing, and number of exacerbations requiring oral glucocorticoids (Table 2).

The initiation of therapy is based on the assessment of severity (Table 3). Patients with intermittent asthma are treated initially with short-acting beta-agonists (SABA) alone. Patients with known triggers are instructed to use beta-agonists about 20 minutes prior to a known trigger such as exercise.[4,9] For a patient with mild persistent asthma, the preferred controller medication is a low-dose inhaled corticosteroid (ICS). If a patient has moderate persistent asthma, the preferred controller medication becomes a low-dose ICS plus a long-acting beta agonist (LABA) or a medium-dose ICS. Severe persistent patients are treated with a medium-dose ICS and a LABA or a high-dose ICS.[4,9] In patients who need additional therapy beyond that described here, providers may consider adjunctive therapy with theophylline,

leukotriene receptor antagonists (such as montelukast), or cromolyn/nedocromil.[4,9] If a patient has severe persistent asthma, anti-IgE therapy omalizumab can be considered if serum IgE levels are within the established range (30-700 IU/mL).[10]

Chronic asthma management relies on assessment and monitoring of functional impairment and response to therapy over time. Impairment is best assessed using a validated questionnaire assessing nighttime awakenings; frequency of as-needed bronchodilator therapy; limitation in home, school, or work activities; and perception of control or peak flow monitoring.[4] One questionnaire that has been validated in the outpatient setting (as well as for home use via mail or telephone) is the Asthma Control Test.[11-14] The history obtained in clinic should assess risk factors for future exacerbations, such as the use of oral glucocorticoids, emergency department visits, hospitalizations, and admissions to the intensive care unit. For patients whose symptoms are not well controlled, a step up in therapy of one level should be performed. Therapy can be continued or stepped down (to minimize adverse effects) in those with adequate control.

Comorbid Conditions

Asthma management should also address comorbid conditions, including gastroesophageal reflux disease (GERD), allergic rhinosinusitis, obesity, and obstructive sleep apnea (OSA). Gastroesophageal reflux disease is common in asthmatics, and treatment may reduce exacerbations and symptoms, particularly in severe asthma.[15] Allergic rhinitis/sinusitis is also common, and treatment may improve respiratory symptoms. Obesity is associated with an increased risk of developing asthma and may be associated with increased asthma severity.[16] Patients with asthma and comorbid OSA should be encouraged to use continuous positive airway pressure (CPAP) with regular compliance (> 4 hours per night on > 70% of nights).[17] Optimally, the goal for CPAP use should be 7 to 8 hours per night. Finally, patients with asthma are at higher risk for depression and other behavioral disorders, which may lead to poor compliance with therapy, adversely impacting disease severity and efficacy of medical care.[18]

Triggers

The avoidance of triggers may reduce the need for controller medications. Inhaled allergens or irritants (tobacco or wood smoke) may be suggested by a history of worsening at home or in the workplace (or during the work week).[9] Allergy testing may be considered for identification of allergens—particularly indoor allergens such as dust mites, animal dander, molds, mice, and cockroaches. Nonselective beta blockers, aspirin, nonsteroidal anti-inflammatory drugs, or dietary sulfites may produce significant exacerbations in some patients with asthma. Administration of the flu vaccine is indicated in all asthma patients, and pneumococcal vaccination is indicated in all adult patients requiring controller medication due to significant risk of complications with pneumococcal infection or influenza.[4]

Patient Education

Patient education is an integral part of asthma management. Patients should be educated on roles of medications, appropriate technique for using a metered dose inhaler and spacer, self-monitoring of disease, identification of triggers and environmental control measures, and a plan for care during exacerbations. Patient education programs have been shown to be effective in reducing hospitalizations.[19] Use of valved holding chambers is preferred.[4] Investigation and education into the role of allergens in the patient's disease is recommended. However, there is insufficient evidence to advocate a single specific avoidance strategy. Comprehensive, as opposed to limited, strategies are recommended. Immunotherapy is effective for patients with persistent asthma and identified inhaled allergen sensitivities.[4] All patients should be queried about smoking history and advised strongly to quit smoking.

Pharmacotherapy

Medications used for asthma primarily include inhaled bronchodilators and ICS when controller therapy is required. Short-acting beta agonists should be used for quick relief of symptoms and can be used preemptively for triggers. The frequency of SABA use should be queried to assess control. In addition, patients should be instructed to seek medical attention should a SABA fail to achieve a quick and sustained response. Inhaled corticosteroids should be used as a first-line treatment to control persistent asthma with initial dosing based on severity. Long-acting beta agonists are the preferred add-on to ICS therapy for patients whose symptoms are not controlled with an ICS. Long-acting beta agonists should not be used for acute symptoms or without an ICS, regardless of asthma stage. They carry an FDA boxed warning regarding increased risk of severe

Table 3. Stepwise Management of Chronic Asthma[9]

Initial Severity	Preferred	Alternative
Step 1: Intermittent	SABA as needed	-
Step 2: Mild	Low-dose ICS	-
Step 3: Moderate	Medium-dose ICS or Low-dose ICS + LABA	Low-dose ICS + LTRA
Step 4: Severe	Medium-dose ICS + LABA	Medium-dose ICS + LTRA
Step 5: Severe	High-dose ICS + LABA Consider oral steroids	Medium-dose ICS + LABA + LTRA Consider referral to specialist
Step 6: Severe	High-dose ICS + LABA + LTRA	Addition of LTRA Refer to specialist

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting beta agonist.

asthma exacerbations and asthma-related deaths.[20]

Leukotriene modifiers may provide benefit and should be used in stepwise fashion as an alternative to LABA in appropriately selected patients. Cromolyn may be considered as alternative to ICS in mild persistent asthma, but is rarely used. Theophylline may be considered if other options have not been successful. Serum levels should be maintained between 5 and 15 µg/mL, and routine monitoring is indicated due to significant toxicities and medication interactions. Omalizumab can be considered as adjunctive therapy in patients with elevated IgE in the prescribed target ranges (30-700 IU/mL) and sensitivity to relevant allergies. In patients with chronic, refractory symptoms, there may be a role for oral corticosteroid therapy outside the setting of acute exacerbations. This decision should be individualized and balance the benefits obtained from therapy against the risks of chronic steroid use (impaired glucose control, immunosuppression, poor wound healing, adverse effects on bone density, and adverse psychiatric effects).

Novel biologic therapies for asthma include antagonists of cytokines interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13), and tumor necrosis factor (TNF)-α inhibitors. These agents have been evaluated in phase 2 and phase 3 studies thus far. The eosinophilic asthma phenotype is described as increased blood or sputum eosinophil levels correlating with disease activity. T-helper 2 cells that express IL-4, IL-5, and IL-13 coordinate eosinophilic inflammation in asthma.[21]

Mepolizumab (anti–IL-5) has been shown to be effective in reduction of exacerbations in patients with eosinophilic asthma phenotype, particularly those with frequent exacerbations.[22] Reslizumab (humanized anti–IL-5) has been shown to significantly reduce symptoms and is currently undergoing phase 3 trials.[21] Benralizumab is a humanized fucosylated IgG1κ monoclonal antibody (mAb) that binds IL-5Rα in order to induce apoptosis in eosinophils and basophils. It is currently under investigation for use in asthma and COPD.[21]

Lebrikizumab (anti–IL-13) has been shown to improve lung function in inadequately controlled asthma patients with elevated periostin levels.[23] Tralokinumab (anti–IL-13 humanized IgG4) improved FEV_1 and reduced symptoms in patients with moderate to severe uncontrolled asthma in comparison with placebo.[24] Pitrakinra is a recombinant IL-4 variant that competitively inhibits the IL-4Rα receptor, inhibiting the function of both IL-4 and IL-13. This agent may prove beneficial in patients with atopic asthma.[21]

Dupilumab, a fully humanized mAb to the IL-4Rα/IL-13Rα receptor complex inhibiting actions of both IL-4 and IL-13 signaling, and has demonstrated > 80% relative reduction in asthma exacerbations, improved symptoms and led to improvement in FEV_1 in patients with moderate to severe asthma and increased serum or sputum eosinophils.[25] It may represent a promising avenue for future asthma research, as its initial investigation has shown both improvement in function and clinical outcomes. Ultimately, ongoing research will be needed to determine the long-term effects of these agents and whether they offer efficacy in asthma patients in general vs specific asthma-phenotypes.

The TNF-α inhibitors have also been investigated for use in asthma. TNF-α is an innate cytokine implicated in chronic inflammatory conditions, including rheumatoid arthritis and Crohn's disease. Macrophages are a major source of TNF-α along with contributions from monocytes, dendritic cells, B lymphocytes, T cells,

neutrophils, mast cells, and eosinophils. TNF-α has a proinflammatory effect on eosinophils, neutrophils, T cells, epithelial cells, and endothelial cells. Studies of asthma have revealed increased TNF-α within respiratory epithelial tissue biopsies and airway lavages of patients with severe asthma compared with those with good control. Etanercept, a soluble TNF-α receptor linked to human IgG1, has been reported to significantly improve symptoms and lung function in severe refractory asthma.[26] However golimumab, an anti-TNF biologic, was shown to have deleterious effects, including an increased rate of serious infections, potential increased risk of malignancy, and 1 death in the treatment group.[27] Identification of the correct patient population may improve clinical outcomes, but a potentially unfavorable risk benefit ratio may limit the future of anti–TNF-α therapy in severe asthma.

CONSIDERATIONS UNIQUE TO THE MILITARY

Active-duty personnel present unique challenges in the diagnosis and management of asthma. Service members should be questioned thoroughly on deployment and exposure history. A significant portion of the current military population has deployed to SWA in the past decade, many for multiple deployments. Research addressing respiratory complaints in the deployed military population is ongoing. To date, military research has demonstrated that while many service members with deployment-related respiratory exposures have a paucity of objective findings after pulmonary medicine evaluation, some demonstrate functional limitations consistent with asthma or airway hyperresponsivenesss.[28] Further retrospective studies did not find a relationship between deployment and diagnosis rates or severity in asthma patients in the Army.[29] A comprehensive evaluation is recommended for service members with dyspnea to include investigating for potential asthma- or exercise-induced bronchospasm, in addition to diagnoses such as vocal cord dysfunction, GERD, and OSA.[28-30]

A recent study in service members with respiratory complaints related to deployment included surgical lung biopsy; however, the clinical applicability of these results is unclear, given the lack of a firm association between the histologic diagnoses and clinical condition of the subjects.[31] In general, it is not recommended to perform surgical lung biopsy for patients with deployment history to SWA in the absence of objective findings on chest imaging or significant changes in pulmonary function testing. Screening spirometry has been postulated as a way to improve monitoring for military members proximate to deployment and longitudinally. However, an unpublished cost analysis estimates that for the over 500,000 active-duty service members, screening spirometry would cost in the tens of millions of dollars.[32] This analysis did not include the costs of follow-up specialty care or further tests. Although screening spirometry does not appear to be feasible presently, research evaluating screening spirometry is in progress in the military.[33]

If diagnosed with asthma, service members should be able to perform all required duties, wear protective gear, and have stable disease requiring infrequent, if any, oral corticosteroid treatment. According to U.S. Army retention regulations, soldiers diagnosed with asthma may be placed on temporary profile (duty restrictions) for up to 12 months when medically advised. If at the end of that trial the soldier is unable to wear a protective mask or pass the timed physical fitness run outdoors (on medications), then the soldier should be placed on a more restrictive physical profile and referred for a medical evaluation board. If able to pass the physical fitness run (or an alternate aerobic fitness event) within standards and perform all military training and duties on ICSs and bronchodilators, the soldier may be placed on a less restrictive temporary profile. If the soldier does not require medications or activity limitations, then no profile qualifications are required. Chronic asthma should also require a physical profile if it results in repetitive hospitalizations, emergency department visits, excessive time lost from duty, or repetitive use of oral corticosteroids.[3]

CONCLUSION

The evaluation and management of asthma in the military requires appropriate diagnosis, treatment, and longitudinal follow-up. The diagnosis should always be confirmed with pulmonary function and bronchoprovocation testing. Conditions mimicking asthma should be excluded, particularly when asthma does not respond to appropriate therapy. It is imperative that patients with asthma who do not demonstrate an expected course of improvement with therapy seek evaluation by a pulmonary disease specialist. This serves to re-evaluate whether the initial diagnosis was correct, assess for potential disease mimics and aggravating comorbidities, and ensure that asthma therapy is in accordance with published guidelines. Service members with asthma can remain on active duty when management with inhaled therapies allows them to meet standards and perform required duties.

Service members with asthma represent a unique and ever expanding patient population, given the role of potential respiratory exposures in SWA. Longitudinal follow-up is critical in conjunction with application of novel therapies as appropriate and understanding the impact of deployment-related respiratory exposures. These patients will continue to require care in the military health care system, the VA health care system, and in the private sector for decades to come. ●

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