2018-2019 Guidelines for Empiric Antibiotic Therapy for Asthma Exacerbation

BACKGROUND

Asthma is a complex upper airway disorder that affects people of all ages. In the United States, over 25 million individuals are diagnosed with asthma, and the prevalence among adults and children is 7.7% and 8.4%, respectively. Moreover, asthma rates are highest among women and black Americans.[1]

Asthma is characterized by recurrent episodes of wheezing, nighttime or early morning coughing, shortness of breath, and chest tightness. Symptoms are usually intermittent and may worsen over time.[2] Depending on the individual, they may become worse at night or with exercise.[3] If left untreated, patients may experience exacerbations, which may require emergency department (ED) visits and hospitalization.[2] In 2016, approximately 10.1% of ED visits were asthma-related, and 189,000 people were hospitalized due to asthma.[1]

Most cases of asthma are idiopathic; however, the strongest risk factor for the development of the disease is the combination of genetics and environmental exposure to irritants. Irritants can include substances like pet dander, dust mites, mold, pollen, tobacco smoke, air pollution, chemicals in the workplace cold air, physical activity, and even certain medications, such as aspirin and beta-blockers.[3]

Several studies have identified genetic variations associated with an increased susceptibility for asthma. Many of these genes are related to immune system function, such as IgE response of B cells or regulatory T-cell function. Other asthma-related genes mediate bronchial hyperresponsiveness, atopy, and elevated IgE levels.[4] Researchers have yet to uncover the function of many novel asthma susceptibility genes, but, it is clear that genetic variations, along with environmental factors, influence the origins of asthma, its severity, and its response to treatment.[5]

Asthma treatment is mainly symptomatic, as there is no cure for the disease. If asthma is managed properly, individuals can have a good quality of life.[3] Diagnosis and treatment is based on asthma severity, lung function tests, and the level of asthma control, which vary from person to person.[6] First, patients are classified as having either intermittent or persistent asthma. If persistent, patients are further classified as mild, moderate, or severe.[6]

All patients should receive medication for quick relief of asthma symptoms. Usually, this is a short-acting $beta_2$-agonist (SABA), which acts as a bronchodilator. Medication adjustment is based on symptom frequency, use of quick-relief medication, and pulmonary function tests.[6] If asthma symptoms persist or get worse despite initial treatment, clinicians may add on further treatment such as an oral or inhaled corticosteroids or a long-acting $beta_2$ agonist (LABA).[1] Likewise, if symptoms improve, medication can also be scaled back or removed from treatment regimens.

Despite optimal medical therapy, asthma patients may experience exacerbations, which are caused by increased inflammatory processes and decreased disease control. Moreover, exacerbations increase disease morbidity, healthcare costs, and loss of lung function.[7] Annually, 1.7 million ER visits, 440,000 hospitalizations, and more than $50 billion in health care expenditures are due to exacerbations.[8] Also, patients who visit the ER or are hospitalized for exacerbations are at a significantly greater risk for future exacerbations, regardless of demographics, asthma control, or asthma severity.[7]

Exacerbations are most commonly triggered by viral respiratory infections with human rhinovirus (RV). Other less common viruses implicated in asthma include respiratory syncytial virus (RSV), coronavirus, adenovirus, and parainfluenza virus.[7] Allergen exposure in the environment, especially indoor allergens, is a significant cause, as well. Pollutants, such as tobacco smoke, particulate matter, such as ozone, nitrogen dioxide, and diesel exhaust can all increase airway hyperresponsiveness and provoke asthma exacerbations.[7] Furthermore, viral respiratory infections can work synergistically with airway pollutants and increase exacerbation risk.[7]

EDUCATIONAL ANALYSIS

Gap #1: Clinicians may be unaware of the current guidelines for the management of asthma exacerbations in the primary care setting

Learning Objective #1: Describe the current guidelines for the management of asthma exacerbations and assess the efficacy of empiric antibiotic therapy during treatment

According to the Global Initiative for Asthma (GINA), an asthma exacerbation is defined as a "change from the patient's usual status that is sufficient to require a change in treatment."[9] In current treatment guidelines, GINA indicates an objective assessment of lung function, controlled oxygen administration, inhaled SABA therapy, and systemic corticosteroid administration.[8] Adjunctive treatment with intravenous magnesium sulfate or a low-density helium oxygen mixture should be used in severe cases unresponsive to treatment.[10] After treating hypoxemia and reducing airway inflammation, clinicians should monitor the response to treatment with repeat measurement of lung function, physical examinations, and pulse oximetry. Upon discharge from the hospital, patients should receive SABA, oral corticosteroids, inhaled corticosteroids, referral to follow-up care, review of inhaler technique, and environmental control measures, if needed.[10]

According to studies, there is a strong correlation between guideline adherence and reduced risk of hospitalization.[11] However, evidence demonstrates limited adherence to guidelines and variation in acute and chronic care in many hospitals nationwide.[8] This is most notable with regards to the use of empiric antibiotics during acute asthma exacerbations.[8] According to GINA, it is not appropriate to prescribe antibiotics routinely for asthma exacerbations.[9] Although bacterial infections can cause exacerbations of asthma, the frequency of this happening is small. Moreover, antibiotics should not be prescribed in exacerbation cases unless there are clear signs, symptoms, and laboratory evidence suggesting a bacterial infection is present.[2]

A recent national survey conducted at 577 hospitals in the United States found that 58.2% of patients hospitalized for asthma exacerbations received empiric antibiotic therapy.[12] Likewise, approximately 18% to 22% of patients discharged from EDs for asthma last year received a prescription for an antibiotic. Researchers concluded that inappropriate antibiotic use in these instances was due to several factors, such as difficulty differentiating bacterial infections from non-bacterial infections, difficulty differentiating asthma from chronic obstructive pulmonary disease in the acute care setting, and knowledge gaps regarding the benefits of antibiotic therapy.[13]

Another study, consisting of nearly 20,000 patients throughout more than 500 hospitals in the United States, determined that antibiotic use in the first 2 days of hospitalization for asthma was common (44%).[8] Additionally, they found that antibiotic use was not associated with better outcomes for patients. In fact, they stated that the use of empiric antibiotics increased hospital length of stay, hospital costs, and antibiotic-related diarrhea risk.[8] Similarly, another study of 681 adults and children hospitalized for asthma, found limited evidence that treatment with antibiotics improved symptoms or lung function tests compared to treatment without antibiotics.[2]

Gap #2: Clinicians may be unaware of the effects of antibiotic misuse and/or overuse on patients and hospital systems

Learning Objective #2: Discuss the consequences of antibiotic misuse and/or overuse on human healthcare and the medical system

The Centers for Disease Control and Prevention (CDC) has stated that approximately 37% of all antibiotic use in hospitalized adult patients is unnecessary; treatment is used for longer than recommended durations or incorrectly prescribed.[13] Furthermore, in approximately 30% to 50% of all cases, treatment

indication, choice of agent, or duration of antibiotic therapy is incorrect.[13] In intensive care units (ICUs) nationwide, 30% to 60% of antibiotics prescribed have been found to be unnecessary, inappropriate, or suboptimal.[14]

Incorrectly prescribing antibiotics to patients can expose them to potential complications, without therapeutic benefits.[14] One study found that 20% of hospitalized patients receiving antibiotics for at least 24 hours had an antibiotic-associated adverse event (ADE). Moreover, another 20% had ADEs due to antibiotic therapy for conditions that did not require antibiotics.[15]

The cause of antibiotic-associated ADEs is largely due to the fact that antibiotics do not selectively target pathogens, but also target nonpathogenic species that help the body maintain homeostasis. This creates an overgrowth of opportunistic pathogens that would otherwise have been limited in number by competing species.[16] One such pathogen is *Clostridium difficile (C diff)*, which causes pseudomembranous colitis; recurring diarrhea that can progress to sepsis and death. According to the CDC, people who are taking antibiotics are 7 to 10 times more likely to contract *C dif.* if taking antibiotics for more than a week.[14] Other common ADEs include allergic reactions, end-organ damage, and infections caused by antibiotic-resistant organisms.[15]

Furthermore, avoiding unnecessary antibiotic therapy also decreases the threat of creating resistant bacterial strains.[17] According to researchers, the overuse and misuse of antibiotics have created an antibiotic resistance crisis.[17] The World Health Organization (WHO) states that antimicrobial resistance is the ability of a microorganism, such as bacteria, to prevent an antimicrobial from attacking it.[18] This results in standard treatment becoming ineffective and, through genetic exchange between bacterial species, the spread of resistance.[19] According to researchers, resistance has emerged to nearly all the antibiotics that have been developed since antibiotics were first introduced in the early 20th century.[20]

Antibiotic resistance is a global emergency, as it has resulted in the spread of multi-drug resistant bacterial species.[18] Drug resistance has correlated with increased morbidity and mortality among patient populations.[18] The CDC estimates that nearly 2 million patients a year get infected with antibiotic-resistant bacterial strains, and approximately 20,000 people a year will die from these infections.[21] Additionally, according to the WHO, antibiotic resistance increases the cost of healthcare for patients because of the longer duration of illness, additional tests, and the use of more expensive drugs.[20] According to researchers, antibiotic resistance forces physicians to use antibiotics that are more toxic to patients and more expensive, because first- and second-line medications are ineffective.[22]

According to one study, appropriate antibiotic use can decrease the hospital length of stay (LOS) for patients with suspected bacterial infections.[23] The study defined appropriate therapy using six criteria, one of which was the administration of empiric antibiotic therapy following national guidelines. The researchers note that decreased LOS positively correlates to better patient outcomes and decreased hospital costs.[24] Conversely, another study found that inappropriate antibiotic treatment leads to prolonged LOS and increased hospital costs.[24]

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CONCLUSION

Asthma is a complex airway disease that, despite optimal medical treatment, can result in worsening symptoms. An exacerbation is classified as a change from the usual state of disease that requires a change in treatment. Physicians must be informed as to the proper guidelines for the management of asthma exacerbations. Optimal treatment of exacerbations requires treatment of hypoxemia and reducing airway inflammation with proper follow-up care. Guideline adherence in asthma exacerbation results in better patient outcomes. Examining the role of antibiotics during an exacerbation will help clinicians avoid unnecessary treatment. Furthermore, evaluating antibiotic efficacy for the treatment of asthma exacerbation will help underscore the need for guideline fidelity. Lastly, illustrating the risks of antibiotic overuse and/or misuse will help physicians avoid mistakes that jeopardize patient care, hospital systems, and the future of health care, both nationally and globally.

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