Acute severe asthma

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Introduction

Acute severe asthma is one of the most common causes of visits to hospital emergency departments worldwide and accounts for the greater part of the economic and healthcare burden of the disease.[1]

Failure to appreciate the severity, inadequate emergency treatment, and delay in referral may lead to increased mortality and morbidity.[2] Asthma is the most common respiratory emergency in clinical practice[3,4] and is usually a failure of long-term control therapy. Several guidelines have been written for the management of acute severe asthma, however these guidelines may not have taken into consideration resource-poor areas like sub-Saharan Africa. There is a need for these guidelines to be reviewed and adapted for use in these regions of the world.

Definition

Asthma is best described as a chronic inflammatory disorder of the airways, characterised by episodic dyspnoea, cough, wheezing, and chest tightness. It is associated with hyper-responsiveness of the airways to a variety of environmental stimuli that may resolve either spontaneously or with treatment.[5] Acute severe asthma is an asthmatic exacerbation characterised by persistent dyspnoea that is not relieved by the usual standard therapy with bronchodilators within 30 mins to 1 hour. It also describes a clinical pattern of acute asthmatic attack that is severe enough to persist, despite the patient's optimum use of his/her conventional medication. It is synonymous with, and has largely replaced, the old term status asthmaticus.

Epidemiology

Asthma is one of the most common chronic diseases worldwide affecting 300 million people and is thus estimated to rise to 400 million by 2025. The global prevalence ranges from 1 to 18% in different population groups. Annual worldwide death is put at 250 000, mostly due to preventable causes.[6] In Nigeria, Elegbeleye reported a mortality rate of 6% in Lagos University Teaching Hospital over a 9-year period (1965–1974).[7] Erhabor and Adigun also reported a mortality rate of 4.9% at the Obafemi Awolowo University Teaching Hospital, Ile-Ife over a 10-year period.[8]

There were approximately 1300 deaths from asthma in the UK in 2005. An estimated 75% of admissions for asthma are avoidable and as many as 90% of the deaths from asthma are thought preventable. Most deaths occurred before admission to hospital.[9] Deaths from asthma are increasing in the United States,[10] with asthma-related deaths in the Chicago area increasing from 45 annually in 1979 to 120 annually in 1996.

Death from asthma has been attributed to several causes including:

- poor access to heathcare services;
- late presentation to the emergency department;
- previous intensive care unit (ICU) admission;
- underuse of steroids;
- poor perception of asthma symptoms by patients;
- psychosocial factors;
- presence of co-morbid conditions such as cardiac disease.

Pathogenesis

The clinical expression of asthma is due to four main pathogenetic mechanisms:

- bronchospasm;
- airway hyper-responsiveness to a wide range of common allergens;[11]
- smooth muscle hypertrophy;
- excessive mucous secretion and airway oedema.

The exact cause of these airway changes is not completely understood. However, interaction between genetic and environmental factors is thought to play a central role. The physiological and clinical features of asthma derive from an interaction among the resident and infiltrating inflammatory cells in the airway surface epithelium, inflammatory mediators, and cytokines. The cells thought to play an important part in the inflammatory response are mast cells, eosinophils,[12] lymphocytes, and airway epithelial cells, neutrophils, macrophages, etc. (see Table 1). Each of the major cell types can contribute mediators and cytokines to irritate and amplify both acute inflammation and long-term pathologic changes.

The mediators released produce an intense immediate inflammatory response producing the reactions mentioned above. There is production of thick, tenacions mucuos plugs containing fibrin and eosinophils, which sometimes obstruct the airways due to impaired mucociliary transport.[13]

Physiological response

The resultant effect of the above mechanisms in an acute

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Table 1 Main characteristics of patients with acute asthma with slow or sudden evolution[17]

Type 1, slow progression	Type 2, sudden progression
Slow-onset acute asthma	Sudden-onset asphyxic, brittle hyperacute asthma
Progressive deterioration >6 h (usually days or weeks)	Rapid deterioration <5 h
80–90% of patients presenting to an emergency department	10–20% of patients presenting to an emergency department
Female predominance	Male predominance
More likely to be triggered by URTI	More likely to be triggered by respiratory allergens, exercise, psychosocial stress
Less severe obstruction at presentation	More severe obstruction at presentation
Slow response to treatment and higher hospital admission, airway inflammation mechanism	Rapid response to treatment and lower hospital admission, bronchospasm mechanism of deterioration

setting include:

- an increase in airway expiratory resistance;
- an increase in expiratory time and high volumes of functional residual capacity (FRC);
- increased total lung capacity (TLC) and residual volume (RV);
- decreased FEV^1 (forced expiratory volume in 1 second) and peak expiratory flow.

Dynamic hyperinflation also occurs as a result of gas trapped in the lungs. In very severe asthma, FEV^1 may be reduced to about 33% of its predicted value and the RV increased to about 400% of normal. Airway resistance and compliance are also increased.

These physiological changes result in breathing becoming more laboured – more marked in inspiration. This produces large swings of intrathoracic pressure of up to 50 cmHg during inspiration.[14]

Alteration in blood gases

Hypoxia is usually found in acute severe asthma. It is caused by ventilation–perfusion inequality resulting from continued perfusion of lung segments in which ventilation is reduced because of severe bronchoconstriction.

The diaphragm is also mechanically disadvantaged by hyperinflation of the lungs. During the early phase of an attack, compensatory hyperventilation results in hypocapnia and respiratory alkalosis. With further narrowing, however, the arterial carbon dioxide approaches normal or may increase. An increasing arterial partial pressure of carbon dioxide in a patient with acute asthmatic attack indicates severe obstruction and respiratory acidosis leading to respiratory failure, at which stage urgent intensive care management is required to prevent death.[15]

Evolution of acute severe asthma and triggers

There are two different pathogenic scenarios involved in the asthma attack progression.[16] When airway inflammation is predominant, the patient shows a progressive (over many hours, days, or even weeks) clinical and functional deterioration (type 1/slow-onset acute asthma) (see Table 1).

Upper respiratory tract infections (URTIs) are frequent triggers and these patients exhibit a slow therapeutic response. In addition, they may have allergic inflammation with eosinophils in the airway. In the less common asthma progression scenario, bronchospasm is predominant and patients present with a sudden-onset asthma attack (type 2 or asphyxic or hyperacute asthma), characterised by rapid development of airway obstruction (<3–6 h after the onset of the attack). Respiratory allergens, exercise, and psychosocial stress are the most frequent triggers. Surprisingly, these patients show more rapid and complete response to treatment. Finally they have a predominance of neutrophils in their airways.

Patient assessment

The essential goals are to determine the degree of airflow obstruction, to identify possible exacerbating factors and possible life-threatening complications.

Medical history

This will include determining the time of onset and severity of symptoms (especially compared with previous exacerbations), all current medications, prior hospitalizations, and emergency department admission. Attempts should be made to uncover the cause of the recent exacerbations. Common causes include exposure to extrinsic antigens, severe viral respiratory infections,[18] inadequate or incorrect medications, exercise, emotions, drugs (such as aspirin, NSAIDS, beta-blockers), seasonal variations, etc.

Early warning signs may include nocturnal symptoms of cough, wheeze, and dyspnoea, which are progressive and poorly responsive to bronchodilators.

As the severity increases the patient may manifest a variety of clinical features. These include difficulty with breathing, tachypnoea, the inability to complete sentences, tachycardia, widespread polyphonic wheezes on auscultation, and a peak-flow reading less than 50% of expected or patient's known best reading (see Table 2).

Physiological assessment is essential in all patients with asthma, particularly during an episode of acute attack (see Table 3). The peak expiratory flow rate (PEF) using a peak-flow meter is a simple and useful test for monitoring the patient's progress.[19] The peak expiratory flow meter is inexpensive portable and safe.

The importance of objective assessment cannot be over emphasised. It has been shown that poor perception of

Table 2 Features of severe asthmatic attack

- Diaphoresis
- Dyspnoea at rest
- Audible wheeze
- Talking in monosyllables, unable to complete sentences in one breath
- Agitation
- Tachypnoea respiratory rate >25 cyc/min
- Tachycardia >110 b pm
- Peak expiratory flow 33–50% of predicted
- Hyperinflated chest
- Widespread polyphonic wheezes

Table 3 Features of life-threatening asthma attack

- Confusion
- Exhaustion
- Cyanosis
- Bradycardia
- Feeble respiratory effort
- Silent chest
- Peak expiratory flow <33% of predicted

the severity of asthma on the part of the patient and the physicians is a major factor causing delay in treatment, which may result in increased asthma-related morbidity and mortality. Approximately 55% of patients presenting with acute severe asthma will have values 40% of normal of the PEF and one-fifth will range between 40% and 60% of normal. Generally however, FEV^1 of less than 1L or PEF of less than 120 L/min is indicative of severe obstruction.[17]

A chest X-ray should be obtained to exclude the possibility of life-threatening complications such as pnemothorax, the presence of which may make the attack unyielding to treatment. It could also show evidence of chest infection, which could have been the precipitant of the acute attack.

Pulse oximetry is necessary to measure the oxygen saturation (SPO_2) in all patients with acute severe asthma to exclude hypoxaemia; this also allows monitoring of SPO_2 during treatment which should be maintained at ≥92%. Arterial blood gases measurement should also form part of the assessment of the patient with acute severe asthma,[20] although this is not readily available in many resource-limited countries.

During an episode of acute severe asthma, hypoxaemia and hypocapnia are usually the rule. The onset of normocapnia signifies a worsening state and the presence of hypercapnia indicates respiratory failure which portends a worse prognosis.

Serum electrolytes, particularly potassium, should be measured. Low potassium may be the result of hyperventilation or treatment with bronchodilators. Hypokalaemia can cause diaphragmatic muscle weakness and thus worsen the patient's condition.

Electrocardiogram (ECG) changes are usually nonspecific but may include sinus tachycardia, ventricular strain pattern, and right axis deviation. A reversible P-pulmonale may occasionally be seen due to increase in pulmonary artery pressure caused by severe hypoxaemia.

Management

The goals of management include relieving the severe airflow obstruction to restore normal lung function, correct hypoxaemia, arrest any life-threatening complications, and prevent future relapses.

Oxygen

Oxygen given at high doses and flow rates helps to prevent tissue hypoxia,[21] corrects pulmonary hypertension, and enhances bronchodilation. It should be given as 35–60% of O_2 by nasal canula or face mask until hypoxaemia is corrected.

B2-agonist

Short-acting inhaled B_2-agonists are the drugs of choice to treat acute severe asthma.[6,22] They have rapid onset of action and their side-effects are well tolerated. The ideal route of delivery is via an oxygen-driven nebuliser which ensures that large volumes of B_2-agonist are delivered directly into the airways. In situations where this is not available, a metered dose inhaler with a spacer device can be used. These are effective for delivery of drugs into the airways and are particularly useful in patients who have difficulty coordinating inhalation with a metered dose inhaler alone. Salbutamol[23] (albuterol) is one of the most frequently used drugs in the emergency department. It has an onset of action of 5 min and duration of action of 6 h. Other drugs used include terbutaline and fenoterol. Long-acting drugs are not recommended for emergency treatment. The use of intravenous B-agonist is not advisable because of the severe systemic side-effects.

Corticosteroids

Bearing in mind that asthma is an inflammatory disease and the bronchospasm of acute asthmatic attack is due to an inflammatory condition, steroids are central in the management of acute severe asthma.[24] Oral steroids should be started as early as possible[25] when an acute attack of asthma fails to respond to conventional bronchodilators. Delay may lead to life-threatening complications.

In the emergency room, IV hydrocortisone 100–200 mg every 6 hours and / or prednisolone 30–60 mg should be started. In some instances patient may be extremely ill and not able to take oral steroid. Intravenous therapy should be continued until the patient shows positive signs of improvement after which he can be switched over to oral therapy. Use of inhaled steroids is not universally recommended, but may be useful in some instances[26] where it should be introduced in the recovery phase. It has been shown that under-use of steroids is one of the leading causes of relapse and death among asthmatics.

Theophylline
The use of theophylline/aminophylline should only be for those patients not responding to standard therapy. In this instance a loading dose (in a patient who has not been previously been on theophylline) of 6 mg/kg over 15–30 min should be followed by an infusion of 0.5 mg/kg/h. Measured theophylline blood level is recommended to be 8–12 µg/ml. In patients already receiving theophylline on admission to the emergency department, a serum level should be measured. If the patients require theophylline they should not be given a loading dose, or it may be given at a reduced level. Theophylines have a narrow therapeutic range and have wide interactions with many drugs. In a patient with liver disease, alcoholism, or cardiac disease the dose should be reduced to 0.2 mg/kg/h.

Anticholinergics
Ipratropium bromide[27] is a quaternary ammonium derivative of atropine and is a selective bronchodilator when inhaled. Due to its slow onset of action (1.5–2 h), it is not used as a first-line attack in acute severe asthma. In patients who show marked side-effects when given maximal doses of B-agonist, or who do not respond to its therapy, adding ipratropium bromide is a reasonable option – given in a nebulised form at a dose of 250–500 mcq 6-hourly.

Magnesium sulphate
The use of magnesium for treatment of acute severe asthma was first reported in 1936 by Uruguayan physicians. A suggested mechanism of action is that by inhibiting smooth muscle cell calcium channels, magnesium blocks muscle contraction.

A large multicenter study[28] demonstrated that IV magnesium sulphate only improves pulmonary function when administered as an adjunct to standard therapy (nebulised B_2-agonist and IV corticosteroids) in a very select subgroup of patients.

In general this drug is safe and inexpensive. The usual clinical dose is 1.2–2 g IV over 20 min.

Heliox
Studies have shown that when administered to patients with severe airflow obstruction, heliox,[29] which is a variable combination of helium and oxygen, can reduce both inspiratory and expiratory airway resistance as judged by an increase in the PEF independent of the action of bronchodilators. It has been shown that the effects of B_2-agonist[30] delivered by jet nebuliser to patients with acute severe asthma in the emergency department can be enhanced by inhalation through a heliox delivery system, guaranteeing a high concentration of helium in the inhaled gas.

Additional therapy
Antibiotics
Viral respiratory infections are one of the commonest causes of asthma exacerbation.[31] Common cold viruses such as rhinoviruses are the principal triggers of wheezing. Most patients may thus not require antibiotics. Evidence has however demonstrated an association between bacterial infections, particularly with *Chlamydia pneumoniae,* and exacerbations of asthma.[32]

Antibiotics are often prescribed in acute severe asthma because of an increase in sputum volume or purulence. Sputum that looks purulent may not actually contain polymorphonuclear leucocytes, rather they may contain eosinophils. In those with definite evidence of infection, such as fever or lung consolidation, antibiotics should be given. Anecdotal evidence shows that adding antibiotics may be useful in most parts of the developing world due to poor environmental hygiene.

Mechanical ventilation
Patients who show signs of continued deterioration despite adequate treatment will require mechanical ventilation. The prognosis is better when the decision to mechanically ventilate is made electively, rather than as an emergency when the patient is moribound.[33] Indications for mechanical ventilation are as shown in Table 4.

Mechanical ventilation is, however, not without risk as complications like barotraumas and lung collapse have been reported. Occasionally patients may be inadequately ventilated. It is important that mechanical ventilation be undertaken by experienced medical staff. Patients should continue with the anti-asthma regimen throughout the period of ventilation.

ICU management
Patients with evidence of severe airway obstruction who improve minimally or deteriorate despite therapy should be admitted to an ICU. Indications include worsening respiratory distress, respiratory arrest, altered mental status, SPO_2 <90% despite supplemental oxygen, and a rising arterial carbon dioxide pressure.[6] Essentially a patient requiring ICU admission often requires mechanical ventilation.

Complications
Complications in the management of severe asthma include:
- respiratory failure;
- pneumothorax due to rupture of bullae;
- hypokalaemia, which can occur as a result of hyperventilation;
- the patient rapidly progressing to a catastrophic

Table 4 indications for mechanical ventilation

• Exhaustion
• PaO_2 <6.5 kpal and falling
• $PaCO_2$ >6.5 kpal and rising
• Hypotension (systolic BP <90 mmHg)
• Confusion
• Coma

asthma, despite adequate treatment.

Other complications that may arise from drug therapy include tremor, worsening tachycardia, and hypokaelemia from B2-agonist. Complications from drugs such as aminophylline include vomiting, palpitations, headache, arrythmias, and cardiac arrest.

Monitoring response

Patients require monitoring closely throughout the period of admission. This should include clinical, physiological, and serial blood gases monitoring.

The PEF should be measured every 15–30 min after starting treatment until the patient is stable and PEF should be recorded before and after giving B_2-agonist and at least four times daily throughout hospital stay.

The criteria for discharge are listed in Table 5.

Table 5 Criteria for discharge from hospital[34]

- Patient should have been on discharge medication for 24h and have had inhaler technique checked and recorded
- PEF >5% of best predicted and PEF diurnal variability <25%
- Treatment with oral and inhaled steroids in addition to bronchodilators
- Own PEF meter and written asthma action plan
- GP follow-up arranged within 2 working days
- Follow-up appointment in respiratory clinic within 4 weeks
- Patient linked up with asthma charity organisations

Patient's education

Education is a big principle of current asthma management. The patient should understand their disease process, understand their medication and how to use it, and be able to react to changes in their disease symptoms and/or actual measured peak flow.[35] In resource-poor regions like sub-Saharan Africa, peak flow meters are not widely available or used by the patient population. Attempts should be made to provide peak flow meters at highly subsidized prices for patients and their use encouraged by the physicians and nurses involved in the management of the asthmatics. This will go a long way in helping to prevent acute exacerbations of asthma.

Acute severe asthma is a common medical emergency that is often faced by the emergency physicians. Prompt recognition and proper management of this condition will reduce mortality. Decisions as to whether patients need further interventions, such as mechanical ventilation, should be made early in order to improve the outcome.

References

1. McFadden ER. Acute severe asthma. *Am J Crit Respir Care Med* 2003; 168; 740–59.
2. Gustavo JR, Carlos R, Jesse BH. Acute asthma in adults; a review. *Chest* 2004; 125: 1081–102.
3. Bonshey HA. Relationship of asthma severity to fatalities. In *Lung Biology in Health and Disease*. New York: Marcel Dekker, Inc, 1998; pp 363–85.
4. Bonshey HA, Carry DB, Fahy JV. Asthma. In *Textbook of Respiratory Medicine*. 3rd edn. Eds Murray JF, Nader JA, Mason RJ, Bonshey HA. Philadelphia: W B Saunders, 2000; pp 1247–89.
5. Bel HE. Severe asthma. *Breathe* 2006; 3: 2129–139.
6. National Asthma Education and Prevention Program Expert Panel. *Report II: Guidelines For The Diagnosis And Management Of Asthma*. NIH publication 97-4051. Bethesda: National Institute of Health, 1997.
7. Elegbeleye OO. Asthma death in Nigeria. *Niger Med J* 1978: 8: 449–51.
8. Erhabor GE, Adigun AQ. Analysis of intra-hospital deaths from acute severe asthma. *Niger J Health Sci* 2001; 1: 22–5.
9. Mannix R, Bachur R. Status asthmaticus in children. *Curr Opin Pediatr* 2007; 19: 281–7.
10. Hall JB. Status asthmaticus: Ventilator management plenary presentation. Programs and abstracts of *Chest* 2000: 66th Annual Scientific Assembly Of The American College Of Chest Physicians, And Clinical World Congress In Diseases Of The Chest, Oct 22–26, 2000, San Francisco, California.
11. Barnes PJ. Pathogenesis of asthma. *J Roy Soc Med* 1983; 76: 580–6.
12. Corrigan CJ, Kay AB. T cells and eosinophils in the pathogenesis of asthma. *Immunol Today* 1992; 13: 501–7.
13. Mc Fadden ER. Asthma. In *Harrison's Textbook of Medicine,* 15th edn. New York: McGraw-Hill; pp 1506–8.
14. Erhabor GE. Management of acute severe asthma. *Med Digest* 1995; 21: 5–10.
15. Maltais F, Sovilj M, Goldberg P, Gottfried SB. Respiratory mechanics in status asthmaticus. Effects of inhalational anesthesia. *Chest* 1994; 106: 1401–6.
16. Kolbe J, Vamos M, Fergussion W, et al. Determinants of management errors in acute severe asthma. *Thorax* 1998: 53: 14–20.
17. Rodrigo GJ, Rodrigo C, Hall JB. Acute asthma in adults: a review. *Chest* 2004; 125; 1081–102.
18. Pattemore PK, Johnston SL, Bardin PG. Virus as precipitant of asthma symptoms. *Clin Exp Allergy* 1992; 22: 325–36.
19. RodrigoJ. Predicting response to therapy in acute asthma. *Curr Opin Pulm Med* 2009; 15: 35–8
20. Galdun JP, Paris PM, Stewart RD. Pulse oximetry in arterial blood gas tensions in acute severe asthma. *Eur J Clin Invest* 1980; Feb: 55–62.
21. The British Guidelines on asthma management 1995: review and position statement. *Thorax* 1997: S1–20.
22. *Global Strategy For Asthma Management And Prevention*. NIH Publication 02-3659. Bethesda: National Institutes of Health, 2002.
23. Ballester E, Reyes A, Roca J, et al. Ventilation-perfusion mismatching in acute severe asthma: effects of salbutamol and 100% oxygen. *Thorax* 1989; 44: 258–67.
24. British Thoracic Society. Guidelines for the management of asthma in adults: acute severe asthma. *Thorax* 1992 ; 47; suppl.
25. LM Stein, RP Cole. Early administration of corticosteroid in the emergency room treatment of acute asthma. *Ann Intern Med* 1990; 112: 822–7.
26. Selected clinical evidence on the use of inhaled corticosteriods in acute asthma. *Expert Rev Clin Immunol* 2008; 4: 723–9.
27. Kelly HW, Murphy S. Should anticholinergics be used in acute severe asthma? *Ann Pharmacother* 1990; 24: 409–16.
28. Silverman RA, Osborn H, Bunger J, et al. Intravenous magnesium sulfate in the treatment of acute severe asthma: a multi center randomized controlled trial. *Chest* 2002: 122; 480–97.
29. Manthous CA, Hall JB, Melmed A, et al. Heliox improves pulsus paradoxus and peak expiratory flow in non-intubated patients with severe asthma. *Am J Respir Crit Med* 1995; 151: 310–14.
30. Kress JP, Noth I, Gehlbach BK, et al. The utility of albuterol nebulized with heliox during asthma exacerbations. *AmJ Respir Crit Care Med* 2002; 165: 1317–21.
31. Johnston SL. Viruses and asthma. *Allergy* 1998; 53: 922–32.
32. Allegra L, Blasi F, Centannimi S, et al. Acute exacerbation of asthma in adults: role of chlamydia pneumoniae infection. *Eur Respir J* 1994; 7: 2165–7.
33. Tuxen DV, Anderson MB, Scheinkestel CD. Mechanical ventilation for severe asthma. In *Acute Asthma; Assessment And Management.* Eds Hall JB, Corbridge T, Rodrigo C, et al. New York: McGraw Hill, 2000; pp 209–28.
34. British Thoracic Society. Guidelines on the management of asthma. *Thorax* 1993; 48: S1–S24.
35. Cowie RL, Revitt SG, Underwood MF, et al The effect of a peak flow-based action plan in the prevention of exacerbations of asthma. *Chest* 1997; 112: 1534–8.