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Review Article

Medical emergencies: pulmonary embolism and acute severe asthma

K. Somasundaram[1] and J. Ball[2]

1 Specialist Registrar in Anaesthesia and Intensive Care Medicine, 2 Consultant and Honorary Senior Lecturer in General and Neuro Intensive Care, St George's Hospital, London, UK

Summary

In this, the second of two articles covering specific medical emergencies, we discuss the definitions, epidemiology, pathophysiology, acute and chronic management of pulmonary embolus and acute severe asthma.

Correspondence to: J. Ball
Email: jball@sgul.ac.uk

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In our previous article we covered atrial fibrillation and myocardial infarction; here we review the management of pulmonary embolism and acute severe asthma.

Pulmonary embolism

Pathology

The lungs bring inspired gas into very close proximity with blood to facilitate diffusion of oxygen and carbon dioxide. To achieve this, the lungs have very large (alveolar) epithelial and (pulmonary capillary) endothelial surface areas. This, coupled with in-series pulmonary and systemic circulations, results in a secondary, and arguably neglected, role of blood filtration. Thus, any particulate matter above the average pulmonary capillary diameter of 5–10 μm that enters into the venous side of the systemic circulation is likely to be captured by the lungs, thereby preventing systemic embolisation. Only rarely does the embolic material result in disease. To do so, the embolic material has either to cause severe, proximal pulmonary artery stenosis or obstruction, affect > 30–50% of the pulmonary circulation [1] or contain chemical or microbiological injurious agents.

By far, the most common pathological scenario is venous thromboembolism (VTE) from the lower extremities, originating in the inferior vena cava (IVC) or below. All of the major risk factors for lower extremity venous thrombosis are ubiquitous in perioperative and ICU patients, namely immobility and variable degrees of pro-thrombotic pathologies (surgery, systemic inflammatory response syndrome (SIRS) and/or infection, tissue injury, cancer etc.). In addition, localised venous injury (e.g. femoral venous lines [2]) and a chronic thrombophilic state (drugs, congenital or acquired thrombophilia) may be present. Indeed, so high is the risk that both mechanical and/or medicinal prophylaxis are mandated in these patients.

However, there is emerging evidence that a significant proportion of 'pulmonary emboli' (PE) are actually locally formed pulmonary artery thromboses or pulmonary infarcts. This conclusion comes from studies using limb ultrasound [3], computer tomography (CT) venography [4] (from the IVC to the ankles at the time of CT pulmonary angiography) or whole-body magnetic resonance direct thrombus imaging [5]. In these studies, a venous thrombosis was found in only 50–75% of

patients, raising the question as to where the thrombosis arose in the remaining 25–50%. Whether pulmonary artery thromboses, if indeed this is the pathology, should be treated identically to PE due to VTE, is unknown. In the first instance, these studies suggest that there is a reason to diagnose the presence or absence of VTE in all cases of PE. A rare but recognised cause of pulmonary artery thrombosis is tumour, either local pulmonary artery sarcoma or embolic from tumour extension into the major veins, in particular, renal cell carcinoma.

The principal consequence of a massive PE is acute right heart failure (Fig. 1). The right ventricle (RV) has some capacity to respond to a sudden increase in afterload. The RV free wall can stretch to accommodate increasing end diastolic volume. This RV dilatation will affect and recruit the interventricular septum resulting in its function moving up the Frank-Starling curve of RV systolic performance. In a normal subject (with no RV pre-conditioning), it is estimated that at its limit, this physiological adaptation can generate a maximum mean pulmonary artery pressure (mPAP) of no more than 40 mmHg (a normal mPAP being 12–16 mmHg). However, this adaptation negatively impacts both diastolic and systolic left ventricular function. This, combined with reduced cardiac output from the RV and hence reduced left heart preload, may result in systemic shock. This in turn may reduce coronary perfusion pressure adding a myocardial ischaemic element to the cardiac failure. This is further exacerbated by the loss of the normally continuous RV coronary flow as a result of the increase in RV systolic pressure. The reflex tachycardia associated with this pathophysiology further

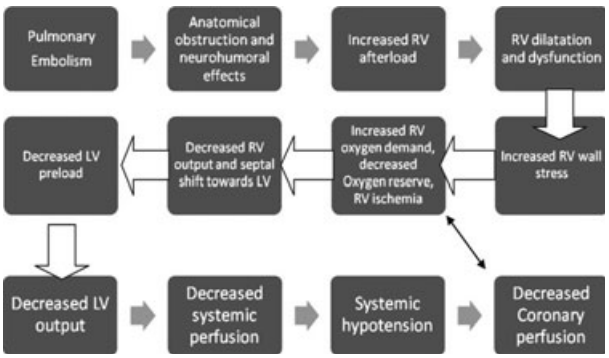

Figure 1 Pathophysiology of pulmonary embolus. Copied with permission from [50]. RV, right ventricle; LV, left ventricle.

reduces coronary flow to both ventricles by limiting the duration of diastole. Failure of this compensatory mechanism is seen to occur over hours to days as a consequence of either increasing thromboembolic burden or cardiac exhaustion or both.

Hypoxia is a secondary consequence of RV failure and ventilation perfusion (V/Q) mismatch. This may be compounded (in ~30% of cases) by an acute, right-to-left, intra-cardiac shunt through the foramen ovale [6]. A classical feature of hypoxia due to PE is a lack of response to oxygen therapy, although this should not negate the importance of this immediate and simple supportive measure.

In patients with acute or chronic respiratory disease, the addition of even a small PE to the overall physiological burden can result in respiratory or RV decompensation or both; although the symptoms and signs are recognised and acted upon, attribution of the event to a PE may be easily missed.

Epidemiology of acute pulmonary embolism due to venous thromboembolism

There is a widely held belief that VTE and consequent PE are underdiagnosed, cause a significant healthcare burden (both acutely, and due to chronic sequelae) and materially contribute to a significant proportion (perhaps 10% [7]) of in-hospital deaths in Europe and the US [8, 9]. Furthermore, it is believed that at least a significant proportion of this burden is preventable. Due to greater awareness, better and more available diagnostic imaging, an ageing population and a growing burden of high-risk co-morbidities, the incidence of VTE and PE is increasing [10], although the proportion of this increase that is attributable to each of these factors individually is unknown.

It is also unknown how many PEs are actually pulmonary artery thromboses, how many patients die with, rather than of, their PE, and how many are preventable. It is well recognised that the diagnosis of an isolated subsegmental PE (~5% of diagnoses) is of questionable clinical significance [1, 11, 12]. It appears that, even with risk prediction tools, only a small minority (10–20%) of patients who have a CT pulmonary angiogram (CTPA) have a PE [13]. As a profession, we are ordering CTPAs out of paranoia [14] and ignoring the radiation dose required, which is equivalent

to 6.2 years of background radiation or 750 chest X-rays [15], a decision our patients may have reason to regret in the future [16].

As a cause of ICU admission, PE is the principal admission diagnosis in only 0.4% of cases [17], a fact that casts yet more doubts over the claim that 10% of deaths occur as a consequence of PE. In the ICU population, the best estimate of the incidence of PE (occurring > 48 h after ICU admission) is that it occurs in 0.5% of cases [17]. The rate of central venous line (superior vena cava or above)-related thrombosis is estimated at anywhere between 10% and 40% [18, 19], although only a tiny proportion of these thrombi appear to cause clinically significant PEs [20–22]. However, if detected, full anticoagulation is recommended whilst catheter removal is not [23].

Diagnosis

The history of a sudden pre-syncopal or syncopal episode associated with hypoxia resistant to supplemental oxygen, in a patient considered to be at risk, is highly suggestive of acute massive PE. Similarly, cardiac arrest with pulseless electrical activity in this context should result in early consideration of blind thrombolysis. However, in the majority of patients, symptoms and signs may be vague or non-specific and lack a sudden, step-wise deterioration. In the peri-operative and ICU settings, the clinical presentation may be easily missed. The only pragmatic advice is always to consider PE as a cause of acute deterioration or failure to respond to supportive care or targeted therapy for an alternative diagnosis.

An important practical question is what to do when the suspicion of a PE exists. The answer is to attempt to give the suspicion a probability. Simple investigations are useful in developing such a probability. As such, a number of considerations should be weighed:

Are there clinical signs suggestive of a deep vein thrombosis (DVT), such as otherwise unexplained asymmetric lower limb swelling? If so, bedside ultrasound to confirm or refute the diagnosis of DVT is worth pursuing, although caution is advised given that 25–50% of patients with PEs have no demonstrable DVT. The alternative of CT venography (IVC to ankles) can be performed at the time of CTPA, without additional contrast, but does expose the patient to a much high radiation dose. This may be justified if ultrasound is negative or unfeasible and anticoagulation presents an unacceptable risk. In this scenario, finding a significant clot burden would result in a clear indication to insert an IVC filter (see below).

Twelve-lead ECG may demonstrate new signs of RV strain [24], although the positive and negative predictive values of such changes are unknown [25]. Suggestive ECG findings include sinus tachycardia, atrial dysrhythmia, dramatic shift in R wave axis, incomplete or complete right bundle-branch block, a QR pattern in lead V_1, infero-lateral ST elevation or depression, inversion of T waves in leads V_1–V_4, and the classic SI Q3 T3 changes.

A plain chest radiograph with no new changes supports the diagnosis of PE, but has an unreliable positive and negative predictive value. However, it may reveal an acute pathology such as a pneumothorax or lobar collapse that warrants specific therapy.

Biomarkers such as D-dimers or fibrin degradation products are elevated by venous thrombosis. However, they are also elevated by surgery, trauma, SIRS, sepsis, cancer and many other pathologies, so while a negative D-dimer assay effectively rules out a significant PE, in the peri-operative and ICU patient populations, there is almost always a reason for an elevated level and hence testing is unhelpful. The degree of elevation appears to have an unreliable correlation with the extent of the clot burden in most studies. However, one large Spanish registry suggests that quantification does predict outcome [26].

Biomarkers of myocardial necrosis, stress and dysfunction may also be of use and are reviewed in our previous article in this Supplement. In the context of PE, newly elevated cardiac troponin (cTn) and B-type natriuretic peptides detect and indicate the degree of RV injury and strain, respectively; hence they estimate severity and are prognostic [1] following PE. Of course, they are not specific to PE, but normal or plateau levels dramatically reduce the clinical probability of acute PE. However, to detect an acute change, there is an argument for daily screening measurement. Whether this can be justified on the basis of cost–benefit analysis is unknown. There is only one study that looked at the kinetics of cTn following PE [27]. This suggests that peak cTn I occurs ~8 h after the event. We can find no

equivalent data for B-type natriuretic peptide kinetics, but, given its shorter half-life, BNP (as opposed to NT-proBNP) is likely to be the more responsive maker with change detectable within 30–120 min. Whether serial BNP accurately tracks evolution of RV dysfunction and the response to therapy is unknown, but is worthy of investigation.

Echocardiography is extremely helpful in determining the clinical probability of acute PE. As with all investigations, a recent previous scan is valuable, if available for comparison. The finding of normal RV size and function does not exclude a small PE, but has a high negative predictive value in massive PE. Echocardiographic findings consistent with, but not necessarily diagnostic of, acute PE include [1]:

- Visible thrombus in the IVC and/or right atrium and/or RV and/or pulmonary artery.
- Acute RV dilatation, defined as end-diastolic dimension on a parasternal view of > 30 mm or a ratio of right to left ventricle (LV) > 1.
- Paradoxical septal motion.
- Moderate-to-severe tricuspid regurgitation, defined as an acceleration time < 90 ms or estimated pressure gradient > 30 mmHg in the absence of RV hypertrophy.
- Right ventricular outflow tract acceleration time ≤ 60 ms in the presence of a tricuspid regurgitation pressure gradient < 60 mmHg [28].
- A pattern of normo- or hyperkinesia of the apical segment of the RV free wall despite hypo- or akinesia of the remaining parts of the RV free wall [29].
- An increase in RV myocardial performance index (tissue Doppler over the lateral tricuspid annulus) with concomitant reduction in peak early diastolic mitral inflow velocity [30].

Definitive imaging

The gold standard for diagnosing PE is multidetector CTPA [11, 31]. However, as discussed above, this investigation is arguably performed with too low a threshold and may be a contributory cause to a future burden of cancer cases. Radionucleotide perfusion or ventilation/perfusion scans and pulmonary magnetic resonance angiography are all reasonable alternatives in ambulant patients, but not in haemodynamically unstable or ICU patients receiving controlled ventilation. In addition to merely detecting or excluding the presence of PEs, CTPA can be used to quantify the pulmonary clot burden [32, 33] and the extent of RV dysfunction (using four chamber reconstruction views RV:LV diameter ratio [31] or volumetric analysis [33]).

Neither of the current pre-CTPA, PE prediction tools [1] is useful or validated in the peri-operative and ICU patient populations [34]. Development of such a tool for peri-operative and ICU patients is needed and should certainly include the presence or absence of a clinical differential diagnosis, cardiac biomarkers and echocardiograph findings.

Treatment

Supportive care is likely to be the first priority whilst a diagnostic plan is formulated and enacted. If hypotension or shock is present and PE or an alternative cause of acute RV failure is suspected, then standard interventions including intravenous fluid boluses, vasopressors and positive pressure ventilation all have the potential to cause further decompensation. In such circumstances, the value of immediate bedside echocardiography cannot be overstated. A simple diagnostic and therapeutic algorithm for the haemodynamically unstable patient has been suggested by the European Society of Cardiology [1] (Fig. 2).

A detailed review of the management of acute RV failure is beyond the scope of this article. We recommend the following recent reviews [35, 36] and summarise their recommendations below:

- Oxygen therapy should be provided and targeted to an S_pO_2 of 92–97%. Although oxygen is a pulmonary vasodilator and might therefore theoretically reduce RV afterload, pulmonary vasoconstriction is not part of the pathophysiology of acute PE. Hyperoxia may cause coronary vasoconstriction; hence aiming for normoxia is recommended.
- Fluid therapy should be guided ideally by reliable continuous cardiac output monitoring, preferably calibrated, and with repeat echocardiograms as clinically indicated. Cautious fluid removal may also be worth considering, again guided by cardiac output monitoring.
- Vasopressor therapy to achieve a reversal of shock and improve coronary perfusion pressure is logical and likely to be beneficial, unless of course the patient is hypovolaemic. Noradrenaline is a logical first choice, but, in theory at least, it is both a pulmonary and systemic vasoconstrictor. If readily available,

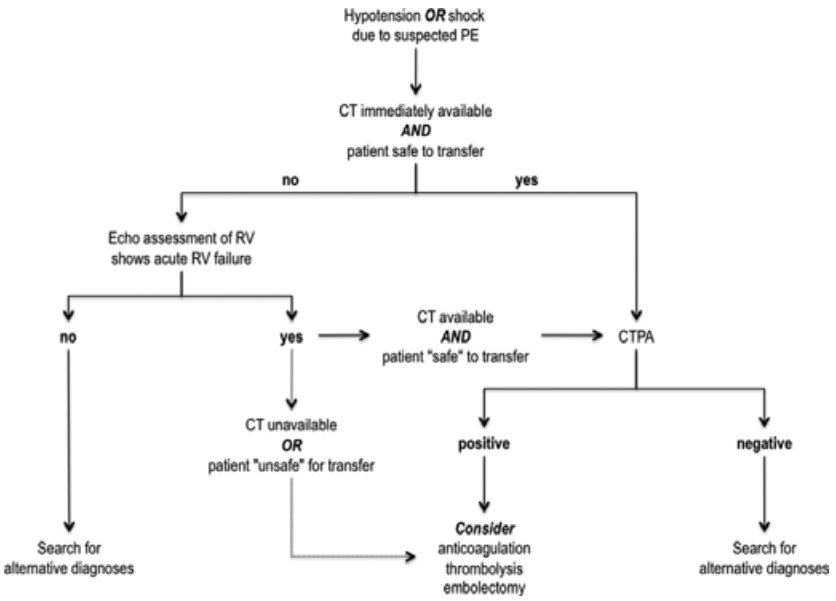

Figure 2 Suggested diagnostic algorithm for pulmonary embolism (PE). Hypotension is defined as a systolic blood pressure < 90 mmHg or an acute drop of > 40 mmHg for > 15 min. The decision as to whether the patient is 'safe' or 'unsafe' for transfer should be made by a senior clinician and based upon multiple patient and local logistical factors. Modified with permission from [1]. CT, computed tomography; RV, right ventricle; CTPA, CT pulmonary angiogram.

vasopressin or terlipressin [37] may be a better first-line therapy as, in theory, they are pulmonary vasodilators and systemic vasoconstrictors.

- Inotropic support for the failing RV is perhaps best achieved using one of the phosphodiesterase (PDE) III inhibitors, milrinone or enoximone. Nebulised delivery of these agents is reliable and possibly superior to the intravenous route. These agents have theoretical benefits over dobutamine. Dopamine and adrenaline are probably poor choices. Given the limited published experience, levosimedan is probably best considered as a second-line inotrope in this clinical setting, the indication being either an inadequate response or failure to tolerate a PDE III inhibitor. A well designed trial comparing a PDE III inhibitor to levosimedan is clearly warranted.
- The use of inhaled or systemic pulmonary vasodilators can be considered in acute PE, but there is no evidence to support their use or recommend any specific agent over another. We would strongly advocate the use of a pulmonary artery catheter to measure the effects of any such therapy directly, and titrate the dose.
- Positive pressure ventilation will cause a decrease in RV preload and an increase in RV afterload in direct proportion to mean airway pressure. Hypoxaemia is best treated using a heated, humidified, high-flow (50–70 $l.min^{-1}$) nasal oxygen system. Hypercapnia is a rare complication of acute PE and although carbon dioxide (CO_2) is a pulmonary vasoconstrictor, experience in acute respiratory distress syndrome suggests that permissive hypercapnia is safe and may even be therapeutic. Unless compromising consciousness, we strongly advise against aggressive attempts to normalise arterial CO_2.
- There are a significant number of case reports of the successful use of RV assist devices and extracorporeal membrane oxygenation in selected patients in the very few centres where these technologies are readily available. As the quality, simplicity and availability of extracorporeal support improves, no doubt more reports of heroic saves will emerge.

Specific therapy for pulmonary embolism

Anticoagulation is the primary therapy for PE. In complex or shocked patients, unfractionated heparin is recommended as first-line therapy with a loading dose of 80 $units.kg^{-1}$ followed immediately by an infusion at 18 $units.kg^{-1}.h^{-1}$. The rate of infusion should be aggressively titrated to achieve an activated partial thromboplastin time of 1.5–2.5 times control. The first test should be conducted 4–6 h after the loading dose and regularly as indicated by dose change [1]. In less severely affected patients, or in those stabilised on i.v. unfractionated heparin, standard regimens of therapeutic dose low molecular weight heparins or fondaparinux

are equally efficacious and do not require monitoring. The pharmacology and reversal issues surrounding the optimal choice in a particular patient are discussed in our previous article on cardiovascular emergencies. It is recommended that therapy is continued for a minimum of five days and that oral therapy with either a vitamin K antagonist, dabigatran or rivaroxaban [38] be commenced at the earliest opportunity and continued for a minimum of three months [23].

Thrombolysis is recommended in patients with proven PE or strongly suspected of having a PE who exhibit persistent hypotension or shock. The recommended first-line choice of agent is recombinant tissue plasminogen activator given either as 0.6 $mg.kg^{-1}$ over 15 min (maximum dose 50 mg) or 100 mg over 2 h. A recent large registry study from the US suggests that thrombolytic therapy reduces mortality but is underused in shocked patients [39]. In patients with relative contra-indications to thrombolysis, prolonged low-dose infusions of thrombolytics have been successfully employed without complications [40]. In normotensive patients, two large retrospective cohort studies [41, 42] and one recent meta-analysis [43] suggest that the risks of thrombolysis appear to outweigh the benefits. However, all recommend a well-designed and appropriately powered, randomised control trial to determine which patients do and do not benefit.

Inferior vena cava filters are considered a second-line therapy in patients with proven PE in whom anticoagulation cannot be safely given, or as a short-term alternative if therapy has to be stopped due to bleeding or to facilitate emergency surgery. A variety of devices are available, either permanent or retrievable. They are notorious for having a high rate of serious complications [44]. There is evidence from registry data in the US to suggest that the addition of an IVC filter to anticoagulation, with or without thrombolysis, may confer a significant reduction in mortality [45]. However, current American guidelines do not recommend this [23].

Percutaneous catheter-based, thrombectomy, thrombus fragmentation, clot pulverisation, rheolytic thrombectomy and rotational catheter embolectomy have all been described in small case series. Currently, these techniques are viewed as experimental, but, if available, may offer the only therapeutic option in an unstable patient with contra-indications to thrombolysis [23, 44]. There is no evidence of benefit or harm from catheter-directed delivery of thrombolytics directly at the thrombus, when compared with systemic administration via a peripheral vein.

Surgical pulmonary embolectomy is a controversial option, the enthusiasm and case fatality rate for which vary dramatically [46–49]. We suspect that this variability principally reflects case selection. As for catheter-based techniques, if they are available and thrombolysis either fails or is contra-indicated, then they should be considered [23].

Follow-up

In patients with a clearly identified precipitant for PE, anticoagulation therapy should be reviewed at three -months. Patients with an 'unprovoked' PE should be investigated for thrombophilia and an underlying pro-thrombotic condition, in particular, abdomino-pelvic malignancy.

At three months, patients with a persistent clot burden on repeat CTPA together with an isolated, significant reduction in transfer factor (on lung function testing) and/or evidence of chronic thromboembolic pulmonary hypertension should be considered for pulmonary thromboendarterectomy [23]. There should also be a risk–benefit assessment conducted regarding life-long anticoagulation and the use of chronic pulmonary artery vasodilator therapy.

Acute severe asthma

Definitions and pathology

All too often, asthma is used as a synonym of dyspnoea [51]. Indeed, so heterogeneous are the phenotypes of what can be referred to as asthma that there have been calls to abandon the use of the term altogether [52]. Attempts to classify the different phenotypes have been the focus of much activity for many years [53, 54]. The differential diagnoses of asthma symptoms and signs are reviewed in detail elsewhere [55]. These range from LV failure to oesophageal reflux [56] to dysfunctional breathing [57].

The natural history of asthma is one of onset in the early years of life with resolution during adolescence [58]. In older adults, the differentiation between late onset asthma and chronic obstructive pulmonary disease

(COPD) often comes down to smoking history. COPD is also a disease with heterogeneous phenotypes, both clinical [59, 60] and pathological/radiological. The latter have historically been divided into a continuous spectrum from isolated chronic bronchitis to isolated emphysema [61]. Notably, there is increasing consensus surrounding the recognition of an asthma/COPD overlap phenotype [62].

Another epidemic of our age that has a complex aetiological relationship with asthma is obesity. Obesity causes changes in pulmonary mechanics, giving rise to symptoms, that are indistinguishable from asthma [63]. In addition, however, obesity results in a systemic pro-inflammatory state that produces a rise in the serum concentrations of a number of cytokines and the soluble fractions of their receptors. Many of these mediators are synthesised and secreted by cells from adipose tissue and have been termed adipokines [64]. The combination of mechanical and inflammatory pathologies results in an asthma phenotype. Perhaps unsurprisingly, weight loss is the most effective treatment.

From a pathological perspective, asthma is a chronic inflammatory disorder that principally affects the later generations of the bronchial tree. It occurs as a consequence of maladaptive immunological responses to environmental aero-antigens. The cause of this maladaptation is multifactorial and includes genetic predisposition and exposure to air pollution and aero-pathogens, principally viruses. It is characterised by chronic inflammation, wall remodelling and hyper-reactivity of the bronchial tree, resulting in inappropriate, variable, inducible and reversible bronchoconstriction with excessive and abnormally viscous mucus secretion. This results in the non-specific symptoms of episodic breathlessness, wheeze, cough and chest tightness. Physiologically, there is expiratory, but not inspiratory, airflow limitation with gas trapping secondary to dynamic hyperinflation [65]. In the context of an acute severe exacerbation, this pulmonary pathology may induce secondary cardiac pathophysiology including large variations in right- and left-sided filling pressures during the ventilatory cycle (pulsus paradoxsus), pulmonary hypertension and consequent RV failure and LV impairment (see PE section, above). This may be further exacerbated by treatment-induced tachycardia and electrolyte disturbances. Indeed, it is the cardiac complications, rather than hypoxaemia, that are the cause of death in fatal cases.

Acute exacerbations of asthma are most commonly defined by worsening symptoms whilst the percentage drop in peak expiratory flow rate (PEFR) from baseline is used as the initial stratification tool for severity [66]. Precipitants of acute exacerbations include [67, 68] upper respiratory tract infections, sudden changes in weather patterns, exposure to air pollution, poor compliance with chronic therapy and psychological stress [69].

Epidemiology

Ignoring the accuracy of diagnosis, chronic asthma is a very common condition in the western world affecting ~10% of adults and ~30% of children [68]. Acute severe asthma is rare and decreasing in incidence [67, 70]; however, it remains a significant cause of preventable death. Most deaths occur before hospital admission and in patients with chronic severe disease [66]. Notably, behavioural or adverse psychological factors and heavy or increasing use of β_2-adrenoceptor agonist therapy are contributory factors in the majority of asthma deaths [66]. A national review of UK asthma deaths (1 February 2012 to 31 January 2013) is currently underway (see http://www.rcplondon.ac.uk/projects/national-review-asthma-deaths).

Acute severe asthma in adults accounts for < 1% of ICU admissions and is decreasing, as is the ICU and hospital mortality [70–72].

Diagnosis

As discussed above, there is a wide and overlapping differential diagnosis for chronic asthma. In adults, acute severe asthma is almost invariably associated with a diagnosis of chronic asthma. Onset of symptoms (principally breathlessness) varies from very acute (minutes) with a clear precipitant to more indolent (days) with no clear trigger. Signs consistent with acute severe asthma include difficulty completing sentences, tachycardia, tachypnoea and a widespread, polyphonic wheeze. Oxygenation is often preserved. Arterial PCO_2 is a useful indicator of severity or exhaustion, a low level indicating the mild end of the spectrum with increasing severity as levels rise through normal to elevated. In older patients or those with more chronic disease, a baseline blood gas may be abnormal and this should

always be considered. Routine investigations should include appropriate blood tests, 12-lead ECG and plain chest radiograph to establish a differential diagnosis, the presence or absence of an additional acute pathology (e.g. lobar pneumonia, pneumothorax) and establish a baseline. PEFR monitoring and/or simple spirometry (the latter being arguably better [73]) is essential to assess severity and response to therapy.

Treatment

There are many mature national and international guidelines for the treatment of acute severe asthma and they present a broad, evidence-based consensus [74]. However, they omit certain, perhaps minor, details we consider important and fail to offer pragmatic advice for tackling the patient who fails to respond to first-line therapies. One of the principal reasons for the latter is the almost total lack of evidence for rescue and second-line therapies. On the basis of a detailed literature search and personal experience, we have attempted to fill this void. The order of interventions listed below is based on a patient with acute severe asthma and no immediate life-threatening airway, breathing, circulation or disability issues.

Actively managing the environment

As detailed above, psychological and behavioural factors are common and important contributors to acute severe asthma. Creating a quiet and calm environment for such patients is essential and is of demonstrable therapeutic benefit.

Oxygen therapy and target saturations

Oxygen should be humidified (and warmed). The fraction of inspired O_2 should be titrated to maintain saturations of 88–95%. The rationale for this is that dry oxygen therapy appears to worsen respiratory function in patients with acute severe asthma [75]. Cold, dry gas is a potent trigger of exercise-induced asthma and damages bronchial epithelium [76]. High levels of inspired oxygen may worsen bronchoconstriction and increase arterial CO_2 levels [77, 78]. If cold or heated humidification is not readily available, continuous nebulisation of either sterile water or 0.9% sodium chloride should be tried. Of note, some types of nebuliser (in particular those using a vibrating mesh) create a very poor aerosol with water. Alternatively, a system using a close-fitting mask with a catheter mount and heat and moister exchanger should be set up, through which supplemental oxygen can be entrained.

Inhaled β_2-adrenoceptor agonists

Effective delivery of 2.5 mg inhaled salbutamol (or equivalent) repeated every 15–30 min up to a maximum cumulative dose of 10 mg over 1 h should be undertaken (in treatment-naïve patients, see side-effects and controversies below).

β_2-Adrenoceptor agonists are rapidly acting (seconds to minutes), potent bronchodilators in treatment-naïve patients. All of the so-called short-acting β_2-adrenoceptor agonists have a duration of action of 4–6 h [79]. The optimal dose and frequency of initial and subsequent therapy are unclear, but the best available data suggest no benefit and increased toxicity for higher doses or frequencies [66, 80, 81]. Low-dose continuous nebulisation (not 'back to back' therapy) can be considered, but requires specialist equipment and is probably of no benefit [82, 83].

A great many factors affect the amount of aerosolised drug that reaches the desired anatomical target; these include the physical characteristics of the aerosol particles (shape, density, charge, mass median diameter and its geometric standard deviation [84]), the physical characteristics of the carrier gas (density and viscosity) and the flow rate and characteristics of the whole generator-to-patient pathway [85]. All delivery systems have a variable and unreliable efficiency with the result that only 10–20% of the aerosol reaches the lower airways; the remainder, in variable and unpredictable proportions, impacts the delivery system, is swallowed by the patient or impacts higher up the respiratory tract. From the latter two sites, a proportion of the drug will enter the systemic circulation [79]. Recommended options for drug delivery include multiple doses from a metered dose inhaler delivered into a spacing device (effective), oxygen-driven jet nebuliser (equally effective), vibrating mesh or ultrasonic nebuliser delivery into a helium oxygen carrier gas with the fraction of inspired helium maximised without inducing hypoxia (most effective) [85].

β_2-Adrenoceptor agonist therapy in the management of acute severe asthma is not without its side-effects and controversies.

Tachyphylaxis to β_2-adrenoceptor agonists (given in isolation) occurs rapidly and cannot be overcome by administration of higher doses [86]. β_2-adrenoceptor agonists cause tachycardia, hypokalaemia, hyperglycaemia and lactic acid production [87]. This combination of side-effects increases both myocardial and respiratory demands and can contribute to decompensation of either or both systems. This may be especially important in acute severe asthma, as patients may have significantly reduced cardio-respiratory functional reserve.

All standard β_2-adrenoceptor agonists are 50:50 racemic mixtures of R- and S- isomers that were developed to emulate the actions of endogenous R-adrenaline. The S-isomer of salbutamol has been extensively studied and has no bronchodilator activity, has dramatically slower clearance and metabolism (especially from the airways) and may be pro-inflammatory and contribute to the desensitisation of the airways to R-salbutamol [88–91]. Furthermore, S-salbutamol exhibits lethal toxicity in equivalent doses to R-salbutamol in animal models. In short, following large doses of racemic salbutamol, the S-isomer gradually accumulates and is toxic. What constitutes a large inhaled dose is unclear, but may be a little as 20 mg over a 4–6 h period.

There is no benefit or evidence of significant harm from giving iv. β_2-adrenoceptor agonists as a rescue therapy to patients with acute severe asthma [66, 92, 93]. So-called long-acting β_2-adrenoceptor agonists have no role in the acute setting.

In view of the possibility of β_2-adrenoceptor agonist toxicity worsening the pathophysiology of acute severe asthma, it is vital to obtain a clear history of dose and frequency of drug exposure. If unavailable, a failure to respond to a further dose of inhaled drug should prompt the suspicion of toxicity contributing to the clinical condition and consideration of withholding further doses for 4–6 h. The diagnosis of beta2 agonist toxicity is further supported by the finding of a lactic acidosis. A proactive supplementation of potassium is strongly recommended.

Inhaled anticholinergics

Immediate co-administration of the nebulised anticholinergic, ipratropium bromide, is strongly recommended [66, 94]. Again, the optimal dosing and frequency regime following this first dose is unknown, but 500 μg 4–6 hourly is generally recommended.

Anticholinergics are comparatively weaker bronchodilators than β_2-adrenoceptor agonists, but there is good evidence of a clinically significant synergistic effect in acute severe asthma [94]. There has been a resurgence of interest in the clinical utility of anticholinergics in asthma and COPD as a consequence of recent advances in the understanding of the pleiotrophic effects of acetylcholine in the lung [95, 96]. Ipratropium bromide is currently the only available nebulisable agent. It has almost no oral bioavailability, the onset of action is < 15 min, with a peak action at 1–2 h and a duration of action 5 h [97]. It blocks all muscarinic receptor subtypes with equal affinity, including the inhibitory neuronal M2 receptors which, in theory, could potentiate vagally induced bronchoconstriction, but probably only at doses greater than those advocated for therapeutic use. Tiotropium bromide, an established long-acting analogue of ipratropium, has functional selectivity for the M3 receptors resulting in significantly greater bronchodilatation. In unresolving acute severe asthma, tiotropium may play a role, but this is yet to be established.

Corticosteroids

Early administration of systemic corticosteroids is essential [66] and synergistic [98] with β_2-adrenoceptor agonists. Either 40 mg of soluble prednisolone orally or 100 mg of i.v. hydrocortisone (6 hourly) should be given. Higher doses have not been shown to be of benefit. Adjunctive use of inhaled steroids at the earliest opportunity, such as 2 mg nebulised budesonide, may be of additional benefit [99, 100].

Corticosteroids are potent anti-inflammatory drugs with a proven track record in acute severe asthma. They exhibit both rapid (non-genomic) and delayed (genomic) effects [101]. The principal rapid effect is airway vasoconstriction and may explain the efficacy of combining inhaled and systemic therapy. The immediate secondary consequences of this vasoconstriction include a reduction in mucosal oedema and increase in airway calibre. They may also have important non-genomic, anti-inflammatory actions.

Systemic therapy should be continued for a minimum of five days or until recovery. Abrupt cessation is recommended [66]. However, systemic therapy should not be stopped prior to reliable delivery of regular inhaled steroids.

Magnesium sulphate

In patients with acute severe asthma who fail to respond adequately to the above therapies, 2 g (8 mmol) $MgSO_4$ should be given over 10–20 min [102]. The value of additional doses remains unknown.

The efficacy of magnesium appears to be limited, although whether this represents underdosing remains speculative. When it works, the effects can appear miraculous, in terms of rapidity of action and degree of bronchodilatation. Magnesium is thought to work principally through bronchial wall smooth muscle relaxation. However, it is also involved in acetylcholine and histamine release from cholinergic nerve terminals and mast cells, respectively. Furthermore, the ability of magnesium to block calcium-ion influx into the bronchial smooth muscle might have therapeutic benefit in acute severe asthma [103]. There is also some evidence that magnesium has an anti-inflammatory role in acute severe asthma [104].

Adrenaline

In patients with acute severe asthma, who fail to respond adequately to all of the above therapies, nebulised adrenaline (0.5–3 mg) may be effective [105]. In addition, or as an alternative, iv adrenaline as a dilute infusion via a peripheral cannula at a dose of 0.25–3 $\mu g.min^{-1}$, titrated to response, may be effective [106].

Adrenaline offers a number of theoretical advantages over β_2-adrenoceptor agonists. Although bronchoconstriction is the major pathology in asthma, airway oedema can also make a significant contribution. As with inhaled corticosteroids, its principal efficacy may be mediated by rapidly reducing laryngeal and tracheobronchial oedema.

Leucotriene antagonists (in addition to corticosteroids)

Recent trials have suggested that there may be a role for iv [107] and even oral [108] leucotriene antagonist therapy in acute severe asthma, but until this is added to updated guidelines, it is unlikely to gain widespread use.

Lidocaine

Lidocaine therapy should be considered as a second line therapy in acute severe asthma. It can be given as a dilute aerosol such as 10 ml of a 1% solution, which depending on degree and duration of response can be repeated approximately every 2 hours. Alternatively, i.v. therapy may be used with a loading dose of 1.5 $mg.kg^{-1}$ over 10 mins followed by an infusion of 1.5 $mg.kg^{-1}.h^{-1}$. If the patient responds, the dose should be down-titrated to the lowest effective dose, with a usual range of 0.25–1.5 $mg.kg^{-1}.h^{-1}$. A high-dose regimen given for a shorter period has also been reported, using a loading dose of 2 $mg.kg^{-1}$ over 5 min, followed by 3 $mg.kg^{-1}$. h^{-1} for 10 min [109].

Lidocaine may attenuate bronchial hyper-responsiveness [109] and has pleiotrophic anti-inflammatory properties [110]. If used as an i.v. infusion for a prolonged period, there is an accumulation of active (hepatic) metabolites necessitating daily cessation to avoid accumulation. Side-effects and toxicity, including myocardial depression and seizures, are extremely rare [111, 112]. Although the role of nebulised lidocaine in chronic severe asthma is limited (at best) [113, 114], we have successfully used it in a small number of cases (unpublished data). In short, lidocaine may or may not be effective, but is non-toxic and may act as a useful adjunct to intubation in acute severe asthma, if this intervention becomes necessary (see below).

Non-recommended therapies

The following therapies have been investigated in acute severe asthma, but have been found to be either useless or harmful:

- Intravenous β_2-adrenoceptor agonists (see above)
- Intravenous theophyllines have been shown to be harmful [115]; despite this, aminophylline remains as a listed rescue therapy in all guidelines [66].
- Nebulised furosemide has not been shown to be of any benefit [116].

Rescue therapies and ventilatory support

Patients failing to respond to the above standard therapies are likely to be severely ill. Consideration should be given to the accuracy and completeness of the diagnosis and the possibility of β_2-adrenoceptor agonist toxicity [117]. There are no guidelines and little, if any, evidence to guide therapy in this situation; hence, what follows is our pragmatic advice.

Helium oxygen-gas mixtures (Heliox) [118]

The efficiency of gas flow is dependent upon, amongst other things, the physical properties of the gas, specifically

its density and viscosity. Reducing the density increases the efficiency of gas flow. Helium is a colourless, odourless gas which is chemically and biologically inert. Its density is seven times less than nitrogen and eight times less than oxygen with a comparable viscosity. Thus, substituting helium for nitrogen in inspired gas mixtures increases the efficiency of convectional and diffusional gas transport. In acute severe asthma, it is only a temporising intervention; i.e. it extends the period of time available for definitive treatment for the underlying condition to be delivered or become effective; it is not, in itself, therapeutic. Helium therapy can dramatically improve dynamic hyperinflation and is very well tolerated. It can be considered an equivalent therapy to mask ventilation, in that it reduces the work of breathing. However, the logistics of obtaining and maintaining an adequate supply can be challenging. Although it can be used as an adjunct to both mask and invasive ventilation, only a very small number of ventilators are capable of safe heliox mixing and delivery.

Medicinal heliox is available in cylinders from most medicinal gas companies in a $He:O_2$ mix of 79:21. It is best administered through a tight-fitting mask. The mask should preferably have a reservoir bag into which the heliox is delivered and one or more one-way expiratory valves. Every effort should be made to minimise air entrainment. Specialist masks and mixing/nebulising circuits are available commercially. Supplemental oxygen can be provided either through a Y-piece mixing circuit or via nasal speculae worn underneath the tight-fitting mask. As its efficacy is proportional to the fraction of inspired helium, this should be maximised. In the UK, standard cylinders contain 1780 l gas, giving ~2 h of therapy at 15 $l.min^{-1}$. Due to its physical properties, it is a superior carrier gas for aerosol delivery, but very poor at generating aerosols through updraft (jet) nebulisers, which are best driven by pure oxygen.

Sedation

Increasing dyspnoea leads to increasing psychological distress, which in turn tends to increase respiratory rate, decrease ventilatory efficiency and worsen dynamic hyperinflation (thereby increasing dyspnoea and worsening gas exchange further). Sedation with controlled depression of respiratory drive may break this vicious cycle and avoid intubation and mechanical ventilation. There is the obvious danger of precipitating acute decompensation and hence the immediate availability of airway and ventilatory rescue is essential.

The choice of agent/s is less important than familiarity with them. Short-acting opioids such as fentanyl, alfentanil or remifentanil are often effective. Propofol probably has some bronchodilatory effect, as has ketamine. The latter has long been quoted as a potential rescue therapy or preferred induction agent in acute severe asthma. However, ketamine can induce dramatic bronchorrhoea in these patients and hence we tend to avoid using it in this setting. Midazolam may be a good choice if anxiety appears to be a major component of the acute crisis. Inhalational anaesthetics can also be effective; isoflurane is well tolerated and is probably a mild bronchodilator. However, sevoflurane may be a mild bonchoconstrictor. We advocate a small loading dose of whichever agent is chosen, followed by low-dose infusion with aggressive titration to response when using intravenous sedatives.

Mask ventilation (non-invasive ventilation)

In a conscious and co-operative patient who is tiring and/or developing hypercapnia, a trial of non-invasive ventilation (NIV) is worthwhile.

To initiate therapy, we recommend that expiratory pressures are set at the minimum level with a low level of inspiratory pressure support that is up-titrated depending upon response and tolerance. Titration of expiratory pressures is a matter of trial and error, with patient comfort and feedback the best guide. Humidification (see above) is highly recommended.

There is never likely to be an adequately powered, randomised trial of NIV in acute severe asthma, nor indeed, we would argue, is such a trial justified. There are a number of studies reporting successful deployment of this strategy [119] and no doubt more will follow.

Intubation

The usual wisdom is, 'avoid intubating if you can but don't leave it to the last minute'. There are as many opinions on this subject as there are options. The safety of the patient is paramount and, given the potential for causing a further acute cardiovascular and ventilatory crisis, the use of a personally favoured and familiar technique is probably the best advice. We favour a slow

induction, with minimal drugs, topical anaesthesia with lidocaine gel, no paralysis and maintenance of spontaneous breathing efforts. It is clearly sensible to avoid giving histamine-releasing neuromuscular blocking drugs (e.g. atracurium and mivacurium).

Invasive ventilation [65, 120]

If invasive ventilation is required, normoxia (or even mild hypoxia [121]) and permissive hypercapnia [122] should be targeted whilst trying to minimise peak airway pressures. Ventilation should start with zero end expiratory pressure, a low respiratory rate (5–10 breaths.min^{-1}), an inspiratory to expiratory ratio ≥1:3 and a peak pressure sufficient to achieve tidal volumes of 4–6 ml.kg^{-1} (ideal body weight). The flow-time curve on the ventilator should be monitored with attempts made to achieve a short period with no flow at the end of expiration. Intrinsic positive end-expiratory pressure (iPEEP) should be measured using either the ventilator's automated function or a manual end-expiratory hold. Unless the iPEEP is zero, incremental then decremental extrinsic PEEP trials should be used, making sure that the iPEEP, trapped volume (if measured) and dynamic compliance are reassessed at each stage. During this process, the peak pressure should be increased to maintain the same inspiratory pressure gradient. Extrinsic PEEP should be set to the optimal level to minimise dynamic hyperinflation and trapped gas volume. If struggling to achieve adequate and safe ventilation, a trial of deep sedation and/or paralysis should be considered. Aggressive weaning from invasive support should be attempted with early extubation followed immediately by the use of NIV or heliox.

Extracorporeal therapies

Both extracorporeal CO_2 removal and full extracorporeal lung assist have been successfully used in very small numbers of patients with acute severe asthma [123]. Given the rarity of the clinical indications for such therapy in this setting and its very limited availability, it should be reserved as rescue for those patients who fail to stabilise with invasive ventilation.

Enhanced immunosuppression

There is no evidence to support the use of enhanced immunosuppression in refractory acute severe asthma.

Recovery and long-term management

As with all chronic conditions, any acute exacerbation should trigger engagement of the team taking on the longer term management of such patients. Such long-term review is vital to try and optimise chronic control, improve functional outcome and reduce the frequency of acute exacerbations and hospital admissions.

Competing interests

No external funding or competing interests declared.

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