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Asthma exacerbations

In their excellent article on asthma exacerbations,[1] Aldington Beasley, ask ''…why there is such a huge discrepancy between the management of severe asthma recommended by evidence based guidelines, and that observed in clinical practice''.

Although the guidelines are in fact quite simple and straightforward, I think that non-specialist junior physicians in the emergency department are confused by the apparent complexity of, for example, fig 3 from their article reproduced from the British Thoracic Society guidelines, especially when faced with an extremely unwell patient with asthma.

For a number of years, I have taught a very simple ''6 P rule'' for the assessment of asthma:

- **P**EFR—baseline and response to first nebuliser.
- **P**ulse, >120 (it is not due to salbutamol).
- **p**O_2 (measure and then titrate oxygen against O_2 saturation).
- **P**anic (ie, ability to speak/respiratory rate).
- **P**aradox (patients cannot sustain this for long).
- **P**neumothorax (make sure the trachea is central until you can obtain a chest *x* ray; and do not allow *anyone* to put in a subclavian line).

This is the basic information needed to assess severity, and decide on management, and it is more easily taught and remembered than a complex figure.

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Authors' reply

We appreciated Professor Woodcock's comments and practical suggestion of the 6P rule as a quick and simple method for assessing asthma severity. We consider that the crucial issue in considering assessment tools is whether their use results in an appropriate therapeutic response. This can be achieved if assessment tools are directly linked to guidelines for management, which is the approach recommended in the British Thoracic Society algorithm (see fig 3). In this way, management is dictated by the results of the assessments made. Thus while the 6P rule is certainly quick and easy to remember, an appropriate decision will still need to be made, and the British Thoracic Society algorithm represents an ideal system to achieve this outcome.

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Innate immune activation in neutrophilic asthma

We would appreciate the opportunity to comment on the very interesting recently published paper by Simpson and colleagues,[1] putatively describing innate immune activation in a ''neutrophilic variant'' of asthma, in inhaled corticosteroid (ICS) treated patients. We feel that the paper is especially important and effective in highlighting the heterogeneity of airway cellular infiltrates in asthma, especially after exposure to corticosteroid.

We endorse the proposal that neutrophils are involved pathogenically, even in stable asthma. This is likely to be the case even when neutrophils are not grossly elevated in number, and indeed they may be at least as relevant as eosinophils across the board, as suggested in early bronchoscopic studies.[2] In these published data, neutrophil cellular activation, and also macrophage activation, were more marked than their absolute number suggested, even in patients with relatively mild, stable asthma.

Cumulative studies suggest that the role of eosinophils has perhaps been over emphasised in the airways of patients with mild, non-ICS treated asthma. Because eosinophils are so absent generally in normal control data, they give a very strong average signal in asthma. They also decrease markedly in numbers generally with ICS treatment,[3] although symptoms and bronchial hyperresponsiveness may persist. We found it interesting that in the data presented by Simpson and colleagues,[1] the actual numbers of sputum eosinophils in absolute terms in ''neutrophilic'' asthma were just as elevated as they were in their ''eosinophilic'' group. The former sputum samples were generally much more cellular and so the eosinophil percentage was found to be markedly lower. It is difficult to know if this is the more relevant end point to focus on.

Many asthmatic airways are acellular even under baseline conditions, and become even more so with ICS treatment,[3] as Simpson and colleagues[1] point out. This fact tends to get overlooked when using mean data for statistical purposes. The response to ICS therapy is also variable, and some individuals with asthma given ICS show an increase in airway neutrophils[4]; it may be this variant that Simpson and colleagues are describing.[1] Their ''paucigranulocytic'' group may reflect the more general trend to become less cellular with ICS.[3] Interestingly, we have previously found that long acting β_2 agonists had an antineutrophilic and especially an anti-interleukin 8 effect on airway inflammation,[4] which may explain some of its added value in combination with ICS.

Simpson and colleagues[1] did not find an elevation in soluble CD14 in sputum in neutophilic asthma, as an index of innate immune activation, as we have previously in bronchoalveolar lavage in post-lung transplant bronchiolitis obliterans syndrome, where bacterial infection is likely to be part of the pathogenesis.[5] We wonder whether the increase in toll-like receptor mRNA that they describe could not just reflect the corresponding increase in absolute number of neutrophils and macrophages which carry these receptors? Although Simpson and colleagues[1] raise some highly pertinent issues, many of the questions that arise from their cross sectional study will inevitably need further longitudinal interventional studies.

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Repeated thrombolytic therapy after initial unsuccessful thrombolysis in massive pulmonary embolism

In patients with massive pulmonary embolism threatened by haemodynamic instability, thrombolytic treatment is recommended.[1] But when it fails, therapeutic options remain limited and are mainly guided by local expertise. In the current case, we report a potential treatment modality for this situation.

A 60-year-old male patient collapsed several times at home. He had a history of a curative left upper lobe lung resection 2 months previously because of a squamous cell lung carcinoma. On admission he suffered from severe dyspnoea. Physical examination showed an elevated central venous pressure and a systolic fixed splitting of the valve sounds. His systolic blood pressure was just below 80 mm Hg, with a pulse of 122 bpm. Thoracic CT angiography (angio-CT) confirmed suspected massive pulmonary embolism (fig 1A) with an increased right ventricular diameter/left ventricular diameter ratio (RV/LV ratio) of 1.76. Because of haemodynamic instability, he received thrombolysis with alteplase (10 mg bolus, 90 mg/2 h), which stabilised his systolic blood pressure at around 100 mm Hg, and then was commenced on nadroparin and coumarins.

Despite thrombolytic treatment, he still had severe orthostatic hypotension, and 5 days after the initial event he collapsed again. Repeat angio-CT showed the same configuration of pulmonary embolism (fig 1B), with an RV/LV ratio of 1.57. We thereafter started treatment with urokinase using an initial bolus infusion of 2000 IU/kg and continuous infusion at 2000 IU/kg/h for 48 h; in the meantime, nadroparin was continued. Within the first 24 h, the patient's clinical condition did not improve but at 48 h he had neither symptoms of orthostatic hypotension nor resting tachycardia. Angio-CT after 48 h of urokinase treatment showed no signs of residual central embolism (fig 1C) and a decrease in RV/LV ratio to 1.12, indirectly indicating a decrease in right ventricular overload. Four days later the patient was discharged.

To date, apart from a very small (n = 8) randomised trial, there is no solid scientific evidence for using thrombolytic agents in the treatment of patients with haemodynamic instability due to massive pulmonary embolism.[2] This worsens when treatment fails in this situation, which has been reported to occur in up to 8% of patients.[3] When initial thrombolytic treatment fails, surgical rescue embolectomy, interventional radiology or using a second thrombolytic drug remain treatment options.[1] Recently, a single centre registry showed that rescue embolectomy resulted in lower inhospital mortality compared with treatment with a second thrombolytic drug.[3] In this study, the second attempt to achieve thrombolysis was performed with either streptokinase or alteplase, depending on which drug had been given previously, but only for a 2 h period. Based on this evidence, the alternative treatment option in our case would have been surgical pulmonary embolectomy which, in skilled hands, has a 1 year survival rate of 86%.[3 4] However, because of the patient's recent thoracic surgery as well as the availability of an alternative treatment option, we decided not to perform surgery.

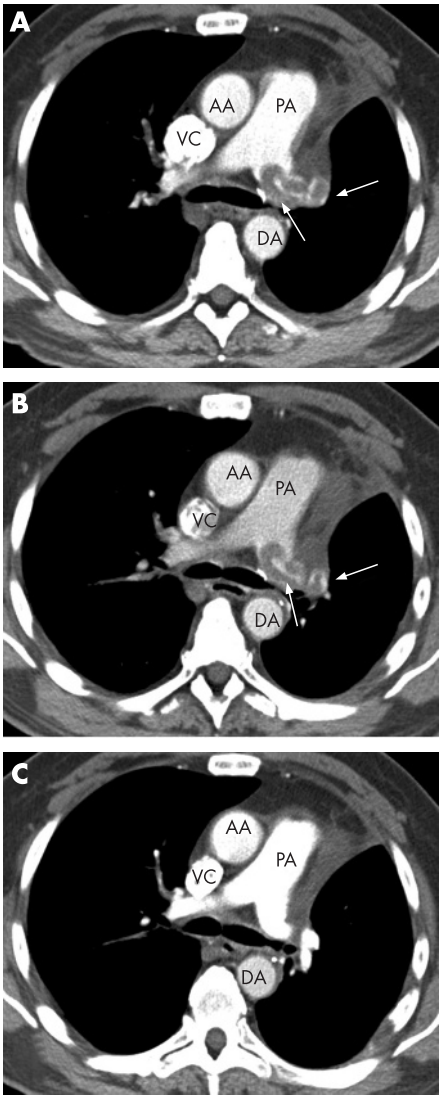

Figure 1 (A–C) Selected pictures from CT angiography (angio-CT) at the main pulmonary artery (PA) level. (A) On admission. (B) Five days after alteplase treatment. (C) Forty-eight hours after initiation of urokinase treatment. Note: the patient had a lobectomy of the left upper lobe (see text). AA, ascending aorta; DA, descending aorta; VC, superior caval vein. The white arrows indicate the actual pulmonary embolism at this section of the angio-CT.

In our case, we choose to give urokinase for a prolonged period, considering the short half life of thrombolytic agents (alteplase 4–6 min, urokinase 4–20 min, streptokinase 18–23 min) as well as the fact that alteplase in a 2 h regimen might be too short to achieve lysis of an extensive clot. Although the effectiveness of prolonged alteplase (24–72 h) for venous thromboembolic disease has been reported, we choose a different agent because of its reported initial ineffectiveness in our patient.[5] In addition, our preference for urokinase over alteplase was related to our previous experiences with this regimen and its known capacity to induce thrombolysis in longstanding clots.[6]

Prolonged thrombolytic treatment in patients with massive pulmonary embolism, who fail to respond to initial alteplase therapy, might be considered a good treatment alternative.

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Bronchial hyperresponsiveness (BHR) and physical activity

We read with interest the recent paper by Shaaban *et al*[1] who report a negative