Pulmonary embolism guidelines: will they work?
A C Miller, D A R Boldy

Updated guidelines on the management of suspected acute pulmonary embolism are published in this issue of Thorax. CT pulmonary angiography has become the central imaging investigation in the diagnosis of pulmonary embolism, but it is important that its use is carefully controlled to avoid unnecessary investigations in overworked radiology departments.

Two years ago several members of the British Thoracic Society independently suggested that, in the light of recent publications, the Standards of Care Committee should update their 1997 advice on suspected acute pulmonary embolism (PE). This issue of Thorax contains the results of this endeavour, with evidence sufficiently robust now to allow these to be called guidelines (see pp 470–83). Those familiar with the previous publication, to which the new document frequently refers, will recognise that the same basic structure has been used.

Previously, the main recommended option in the face of a non-diagnostic ventilation-perfusion (V/Q) scan was pulmonary angiography, an invasive test that was little used before and probably little more after. This advice has been made redundant by developments in CT pulmonary angiography (CTPA), with strong evidence that, even though a negative result may not entirely exclude PE, it does make anticoagulation unnecessary. There is no doubt that CTPA should now be considered the central imaging investigation in suspected PE, and many acute hospitals are developing experience of the techniques.

However, this adds a considerable workload to radiology departments already struggling to cope with the increased imaging requirements for cancer staging, not helped by the fact that PE is confirmed in only 20–35% of those where it has been suspected. This has led to different strategies for reducing the number of unnecessary CTPAs, but these too have their problems.

Some hospitals continue to use V/Q scanning as a way of obtaining a definite answer, but 30–50% of such patients will require CTPA anyway, which delays definitive investigations and lengthens hospital stay, and others do not have nuclear medicine on site. Indeed, were CTPA easily and rapidly available, V/Q scanning would become largely obsolete.

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Another approach is to restrict CTPA to patients who do not have the combination of low clinical probability and a negative D-dimer test. Since this halves the number requiring lung imaging it is an attractive option, but practical experience shows that there are pitfalls. Firstly, although the 1997 clinical probability assessment system has been retained (now on good evidence), the fact that it is very simple does not mean that junior doctors use it properly, as many senior clinicians and radiologists have discovered. Secondly, the seductive simplicity and low cost of D-dimer assays mean that, in many emergency departments, the test is done on a high proportion of patients who arrive with chest pain and/or breathlessness, even when another diagnosis is obvious, similar to the way that cardiac enzymes are often misused. The end result is that, where the D-dimer test happens to be positive, it is assumed that this makes PE more likely after all.

For these guidelines to work in practice without widespread abuse of the recommendations, the following policies should be introduced:

1. Clinical probability must be recorded in the admission notes and be included on every request form for CTPA, a policy that would be fruitful to audit regularly.
2. D-dimer tests may only be requested by junior doctors with at least 6 months post-registration experience of acute medicine. They should not be performed when CTPA is required anyway.
3. Request forms for CTPA which do not state clinical probability and (where appropriate) D-dimer results are automatically rejected by the radiology department, accompanied by a strong telephone message.
4. Where V/Q scanning remains part of the hospital’s management algorithm, there should be a system in place whereby an inconclusive result leads to an automatic CTPA on the same day, without a further request having to be generated by the clinician.
5. There should be at least one interested physician and radiologist who together review and refine both the hospital’s policy and its application in practice.

These principles might appear draconian and unenforceable, yet several hospitals have been adopting them successfully for some time, finding that they stimulate good clinical thinking, reduce the number of unnecessary imaging tests, speed up the process of reaching a correct diagnosis, and are educationally valuable. Indeed, with the widespread changeover from unfractionated to low molecular weight heparin, an increasing number of patients are being quickly investigated and, where necessary, managed without being hospitalised.

Although the document is aimed primarily at junior physicians in UK Accident & Emergency departments, almost all the underpinning evidence comes from continental Europe and North America. Allowing for variations in resources, organisation and clinical practice in different countries and debates around interpretation of current data, it broadly reflects current international thinking and should prove useful elsewhere.

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Nicotine replacement therapy in smoking cessation

I Campbell

Evidence for benefit from nicotine replacement therapy in hospital patients is inconclusive, although the results of a trial reported in this issue of Thorax give cause for optimism and should stimulate further studies.

Most smokers become nicotine dependent and, when they stop smoking, experience withdrawal symptoms and craving. Nicotine replacement therapy (NRT) reduces these unpleasant symptoms and, theoretically, should decrease the risk of relapse. Smoking cessation is properly defined as validated sustained abstinence from cigarettes and/or other tobacco products for at least 6 months, but preferably for 1 year. This editorial includes evidence only from those studies which have applied such a definition and which have specified their settings and populations.

NRT is available as chewing gum, transdermal patches, sublingual tablets, lozenges, inhalation cartridges and nasal spray. In specialised cessation clinics\(^1\) and in primary care,\(^{10} \) prospective randomised clinical trials have shown that NRT, used as an adjunct to advice and support, results in better cessation rates than those of advice and support alone. In the clinics success rates with NRT tend to be higher (11–30%) and more consistent than in primary care, where some studies have found no significant difference from placebo.\(^{11-14} \) One study in primary care showed 8% success with nicotine chewing gum compared with 4% with advice plus leaflet, but there was no placebo controlled arm.\(^{12} \) Two studies of transdermal nicotine in primary care have shown success rates of around 10%, which were superior to those with placebo (around 6%).\(^{15-16} \) The benefit for transdermal nicotine in cessation clinics\(^8\) and in primary care\(^9\) is thus clear, whereas nicotine chewing gum,\(^5\) inhaler,\(^7\) nasal spray,\(^6\) lozenges\(^5\) have only proved superior to placebo in cessation clinics. Success rates of 15–28% have been reported with nicotine patch (5 months) and nasal spray (12 months) producing better results than nicotine patches alone.\(^7\) In a comparison of dosages, the large European CEASE trial reported a greater effect with a 23 mg patch (15.4% success) than with 15 mg (13.7% success, p<0.03),\(^3\) but in the USA Jorenby et al\(^8\) found that a 44 mg patch did no better than 22 mg. The 24 hour patch and the 16 hour patch produced similar quit rates;\(^8\) using the patch for 22 weeks rather than 8 weeks did not significantly improve the success rate.\(^8\) In highly dependent smokers nicotine gum in a dosage of 4 mg was better than 2 mg;\(^3\) 5–20% of smokers can become addicted to nicotine gum.\(^3\)

This appears to be less of a problem with transdermal nicotine\(^1\) and more of a problem with nasal spray.\(^7\) Unwanted effects have tended to result from local irritation but occasionally—usually in those who continue to smoke while using NRT—systemic effects of excessive nicotine can occur (chilliness, nausea).\(^6-8\) In pregnancy and in patients with myocardial infarction NRT, which delivers less nicotine than cigarettes and no carbon monoxide, is less hazardous than continued smoking but, nevertheless, there is still reluctance to use it.

NRT is now available in the UK on NHS prescription. Smoking cessation counsellors have been employed by the NHS to provide advice and support in the community to smokers who self-refer or are referred by other health professionals. NRT is usually offered as part of the package. The sustained validated 6 month or 1 year quit rates achieved through this service are eagerly awaited. These results should not only inform local health groups, primary care trusts, and government of how cost effective the service has proved and how best to shape it in future, but should also make an interesting comparison with the results obtained in the clinical trials.\(^3\)

For hospital inpatients and outpatients the evidence for the efficacy of NRT as an adjunct to advice and support is not convincing. Many reports stemming from cessation services located in hospitals have been wholly or partly based on populations of self-referred smokers or smokers recruited via the media. Such populations differ in motivation and other aspects from patients who, despite presenting to secondary care, continue to smoke. Their quit rate should not therefore be taken as representing the quit rates of populations of patients. The first randomised trial of NRT in hospital patients in the UK enrolled 1550 inpatients or outpatients with smoking related diseases (SRDs); neither nicotine chewing gum nor its placebo significantly improved on the success rate of 9% achieved by brief advice from the hospital physician and follow up in an outpatient clinic at 3, 6 and 12 months.\(^9\) This success rate is little different from the 11% reported from Nottingham by Molynex et al\(^10\) in this issue of Thorax in a study of hospital inpatients which was not restricted just to those with SRDs. Interventions compared were: (a) usual care, (b) 20 minutes’ bedside counselling by a research doctor or nurse trained in smoking cessation counselling plus an advice leaflet, and (c) 20 minutes’ bedside counselling by the same personnel plus 6 weeks of NRT. Patients were allowed to choose one of five forms of NRT, 63% electing transdermal nicotine. They were reviewed in outpatients or interviewed by telephone 3 and 12 months after entering the trial. Exhaled air carbon monoxide was used to validate claims of abstinence. In the usual care group 7.6% were classed as successes (continuous abstinence) compared with 4.4% in those receiving counselling plus advice leaflet and 11% in the counselling plus NRT group (p=0.25). Thus, like a previous trial by Campbell et al\(^10\) of transdermal nicotine plus counselling in 234 hospital outpatients and inpatients with SRDs which showed 21% success with active versus 14% with placebo patches (p=0.15), there was a suggestion that NRT was of benefit but smaller than expected sample sizes have limited the power to detect differences caused by treatment rather than chance.

Previous trials of NRT and counselling in hospital patients with SRDs have included a group given NRT placebo,\(^16-18\) a design feature missing in the Nottingham study. Nicotine chewing gum was no more effective (20% success) than placebo in a study of 219 inpatients,\(^19\) nor was transdermal nicotine (14% success) better than placebo in 584 outpatients with ischaemic heart disease.\(^20\) In a more recent outpatient
trial conducted among 245 hospital inpatients and outpatients but excluding patients with recent myocardial infarction, advice and support plus the combination of regular transdermal nicotine and as required nicotine inhalator resulted in a success rate of 16% compared with 14% for advice and support alone. Higher success rates have been achieved in the hospital trials which provided more intensive support during the first weeks after quitting than was provided in the Nottingham trial. For hospital patients the evidence for benefit from NRT as an adjunct to advice and support (minimal or intensive) remains inconclusive, although the trial by Molyneux et al gives cause for optimism.

Guidance on the use of NRT and bupropion for smoking cessation was issued by the National Institute of Clinical Excellence (NICE) in March 2002. It is likely that UK hospitals will appoint smoking cessation counsellors to provide advice and support in conjunction with NRT or bupropion, as recommended by NICE. It is important not only that the success rates of these programmes be properly evaluated, but also that there should be further placebo controlled clinical trials of NRT in hospital patients. Such trials are both justified and desirable.


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ADAM 33: just another asthma gene or a breakthrough in understanding the origins of bronchial hyperresponsiveness?

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ADAM 33, the latest of the ADAM proteins to be described, has been identified as a major susceptibility gene in asthma linked to bronchial hyperresponsiveness. It provides an important breakthrough in our understanding of this complex disorder and its variable clinical and physiological presentations.

Asthma is a disorder of the conducting airways in which Th2 mediated inflammation interacts with structural changes to cause variable airflow obstruction. Fundamental to disordered function is the concept of bronchial hyperresponsiveness (BHR) in which the airways constrict too much and too easily. In chronic severe asthma the inflammation and structural changes both become more intense and are paralleled by an increase in BHR that is only partially or non-responsive to treatment with corticosteroids. Excessive velocity of contraction linked shortening, treatment with corticosteroids, is only partially or non-responsive to are paralleled by an increase in BHR that is.

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including TGF-β, whose release from bronchial epithelial cells is increased in response to epithelial damage and airway inflammation. Asthmatic (myo) fibroblast cells are unusual in that they have the capacity to proliferate in the absence of exogenous growth factors paralleling the behaviour of asthmatic ASM cells in vitro. This shared trait is consistent with the occurrence of a common stem cell population whose numbers are increased in asthma due to an inherent capacity for enhanced growth and survival.

Members of the ADAM family are proteins with diverse functions that reflect the complex domain structure of these molecules. While certain functions can be attributed to an individual domain—for example, ectodomain shedding to the metalloprotease domain and cell adhesion to the disintegrin domain—it is likely that the other domains play important regulatory roles in these functions by conferring specificity and selectivity. ADAM proteins are anchored in the trans-Golgi network or plasma membrane but, in some cases, secreted splice variants have been identified. In the case of ADAM 12, an evolutionarily close relative of ADAM 33, ectopic expression of the secreted form of the molecule (ADAM 12S) in rhabdomyosarcoma cells results in growth of tumour xenografts which are infiltrated with large numbers of host derived smooth muscle cells. Although we have identified several alternatively spliced forms of ADAM 33 in lung derived cDNA, it is not yet known whether a secreted protein variant is produced by airway cells.

The importance of genetic variation in ADAM proteins has recently been highlighted by mutations in ADAMTS13 (ADAM with thrombospondin type 1 motif) that underlie thrombotic thrombocytopenic purpura, while decreased levels of ADAMTS2 impair collagen type 1 processing leading to fragile skin in Ehlers-Danlos syndrome.

**POSSIBLE ROLE OF ADAM 33 IN ASTHMA AND BHR**

Although ADAM 33 is a highly polymorphic gene containing over 55 SNPs, genetic analyses have identified the 3′ portion of the gene that encodes the transmembrane and cytoplasmic domains and 3′UTR as likely to be the key region linked to asthma and BHR. In the UK population association studies revealed that six SNPs in the ADAM 33 gene were significant at p<0.03, including two (S and S′) in the exon encoding the transmembrane domain (p=0.03 and 0.004, respectively) and another (ST′) which lies in the intron separating the transmembrane and cytoplasmic domains (p=0.02, fig 1). When ST and ST′ were analysed as a haplotype or with SNPs in the intron preceding the V exon, the level of significance greatly increased (p=0.000003–0.0005). Further confirmation that the transmembrane and intracellular domains are key sites for controlling altered functions of ADAM 33 comes from TDT analyses in the UK population. In this case the cytoplasmic S, ST′ and T SNPs occur in a single exon (V) encoding the intron separating the transmembrane and cytoplasmic domain (p=0.0001). When ST and ST′ were analysed as a haplotype or with SNPs in the intron preceding the V exon, the level of significance greatly increased (p=0.000003–0.0005). Additional haplotype analyses increased the significance of the association of this SNP with asthma and BHR when taken in conjunction with the T′, an SNP which causes an amino acid substitution (V→A (one letter code)), showed a significant association with asthma (p=0.0043) and BHR (p=0.0066). Additional haplotype analyses increased the significance of the association of this SNP with asthma and BHR when taken in conjunction with the T′, an SNP which causes an amino acid substitution (V→A (one letter code)), showed a significant association with asthma (p=0.0043) and BHR (p=0.0066). Additional haplotype analyses increased the significance of the association of this SNP with asthma and BHR when taken in conjunction with the T′, an SNP which causes an amino acid substitution (V→A (one letter code)), showed a significant association with asthma (p=0.0043) and BHR (p=0.0066). Additional haplotype analyses increased the significance of the association of this SNP with asthma and BHR when taken in conjunction with the T′, an SNP which causes an amino acid substitution (V→A (one letter code)), showed a significant association with asthma (p=0.0043) and BHR (p=0.0066).
9:Fc fusion protein via α,β causes a very large increase in cell motility, which suggests that the ADAM could act as a local mediator/adhesion receptor. In contrast, overexpression of ADAM 15 decreases cell migration by increasing cell-cell contacts without affecting initial cell adhesion.56

In conjunction with the cysteine rich domain, a novel secreted form of ADAM 12 provokes myoblast fusion in vivo by binding to the muscle specific actin binding protein, α-actinin-2.7 If the equivalent domain in ADAM 33 has similar properties, it could be implicated in converging ASM cells from acting as multiple units to a single contractile unit,8 a property relevant to the pathogenesis of BHR.

CONCLUSIONS

The identification of ADAM 33 as a major susceptibility gene in asthma linked to BHR is an important breakthrough in our understanding of this complex disorder and its variable clinical and physiological presentations. ADAM 33 is the latest of the ADAM proteins to be described,9,57 with its implication in the pathogenesis of asthma being described in the same year. Identifying a major new candidate gene for asthma creates an imperative to determine its function and how disordered function translates into disease. The work ahead is likely to provide important insights into the origins and progression of asthma, especially since expression of ADAM 33 has now been shown in fetal lung tissue. It is not infrequently stated that searching the whole genome for susceptibility genes in complex diseases such as asthma is like “fishing expeditions”. However, as recently pointed out by Ahmad and Goldstein,9 a sequential approach to identifying novel genes in complex disorders by combining linkage and association approaches can achieve success without having to resort to expensive and time consuming genome-wide association mapping. To achieve this in any complex disease it is becoming increasingly appreciated that it is essential to define the disease phenotype accurately. ADAM 33 can now be added to the group of genes involved in Type 2 diabetes (α-amylase 2 (Cronh’s disease)) as an entirely novel molecule linked to the pathogenesis of a complex human disease. The future challenge will be to determine the function(s) of ADAM 33 and the abnormalities that may occur to account for its association with asthma and BHR.

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Allergic sensitisation to peanut may occur through inflamed skin

The increasing incidence of peanut allergy prompted this group to look at the predisposing factors to the condition. A subgroup of 49 children with a clear history of peanut allergy was identified from the Avon longitudinal study (a cohort of 13 971 preschool children). Information was obtained from questionnaires, medical records, and cord blood. Peanut allergy was confirmed by double blind, placebo controlled food challenge in 23 of the 36 children tested. Allergic responses to food challenge included bronchospasm, stridor, and angioedema. Significant associations with peanut allergy were found with soy milk/formula consumption (odds ratio 2.6), family history, and history of atopy. Interestingly, rashes over joints (odds ratio 2.6) and the use of skin preparations containing peanut oils to these rashes (odds ratio 6.8) were associated with peanut allergy. The group hypothesised that allergic sensitisation occurs to peanut antigens through inflamed skin as they are present in emollients used for the treatment of diaper rashes, eczema, dry skin, and inflammatory cutaneous conditions. More trials are needed, however, and, if this is the case, avoidance of exposure to emollients containing peanut oils may prove to be a cost effective therapeutic intervention.

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