Also, in the Glasgow study effective implementation strategies, such as educational interactive meetings and practice visits,⁸ were taken up by only a minority of general practitioners in the intervention group. The use of such strategies was not mentioned in the Aberdeen study, though there was a strong history of research collaboration across the primary-secondary interface.

The novel message of the comparison between the two studies, however, is that a more comprehensive evaluation of the guidelines questions the underlying assumptions about improvements in terms of patient outcomes and reduced costs. Unlike the Aberdeen study, the Glasgow study also measured clinical behaviour in the secondary sector. Despite the increase in the rate of appropriate investigations carried out by the intervention practices, a high proportion of tests were repeated in hospital, even though the results were normal before referral.⁶ There was also no demonstrable difference between control and intervention practices in the number of hospital outpatient appointments needed before the management plan was agreed in secondary care for couples. This lack of the expected changes in clinicians' behaviour in secondary care may also explain the lack of reduction in direct NHS costs.

This disappointing finding might have been avoided if the secondary care professionals had taken part in developing the guidelines. Common clinical problems require shared management between primary care and the hospital teams. The importance of identifying all groups of professionals who may be affected by or who may influence the desired changes in practice cannot be overemphasised.⁵ These groups and individuals must be actively engaged, and specific individual and organisational barriers must be identified and addressed. The Glasgow authors suggest that hospital clinicians may repeat investigations with normal results because they mistrust results from unfamiliar laboratories. This problem could be eased by computerised access to the results of laboratory investigations and the use of high quality standardised laboratory procedures.

More studies are needed that evaluate guidelines in terms of changes in the behaviour of both primary and secondary care professionals. If guidelines on common problems are to deliver cost effective care, appropriate clinical management in primary care needs to substitute for and not to be in addition to traditional hospital management. The Glasgow study

suggests that, perversely, implementing guidelines may lead to a higher overall direct NHS costs per patient referred. Increased venesection and requests for specimens are also likely to have psychological costs for the patients. If the authors had not invested in evaluating these guidelines wider dissemination of the guidelines could have increased NHS costs. Clearly it cannot be assumed that well formulated and implemented guidelines will lead to lower expenditure in the NHS.

The national service frameworks and organisations such as the National Institute of Clinical Excellence (NICE) are leading an increasing tendency to formulate and disseminate national guidance throughout the NHS. If these national initiatives are to lead to improved patient care and more cost effective use of resources, then local implementation and evaluation are required. For common clinical conditions this requires the collaboration of both primary and secondary care health professionals. Increasingly these professionals will include not only doctors but also nurses, physiotherapists, occupational therapists, dieticians, laboratory technicians, and others. Local research expertise should be harnessed to demonstrate changes in practice, and NHS managers need to ensure that these initiatives are properly resourced to ensure rigorous implementation and evaluation of the impact.

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- 1 Woolf SH, Grol R, Hutchinson A, Eccles MP, Grimshaw JM. Clinical practice guidelines: the potential benefits, limitations and harms of recommending how to care for patients. *BMJ* 1999;318:527-30.
- 2 Secretary of State for Health. *The NHS plan*. London: Stationery Office, 2000.
- 3 Secretary of State for Health. *A first class service: quality in the new NHS*. London: Stationery Office, 1997.
- 4 Effective Health Care. *Implementing clinical guidelines: can guidelines be used to improve clinical practice?* Leeds: University of Leeds, 1994.
- 5 Effective Health Care. *Getting evidence into practice*. York: University of York, 1999.
- 6 Morrison J, Carroll L, Twaddle S, Cameron I, Grimshaw J, Leyland A, et al. Pragmatic randomised controlled trial to evaluate guidelines for the management of infertility across the primary-secondary care interface. *BMJ* 2001;322:1282-4.
- 7 Emslie C, Grimshaw J, Templeton A. Do clinical guidelines improve general practice management and referral of infertile couples? *BMJ* 1993;306:1728-31.
- 8 Bero LA, Grilli R, Grimshaw J, Harvey E, Oxman A, Thomson MA. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. *BMJ* 1998;317:465-8.

Preventing exacerbations of chronic bronchitis and COPD

Two recent Cochrane reviews report effective regimens

Papers p 1271

BMJ 2001;322:1259-61

Exacerbations of chronic obstructive pulmonary disease affect quality of life and the cost of managing the disease. Though the long term effects of hypersecretion on the deterioration of ventilatory function in patients with chronic obstructive pulmo-

nary disease have been debated for many years,¹ recent data show a good correlation between hypersecretion and long term deterioration of ventilatory function in these patients.² This is why mucolytics, which seem to have an effect on hypersecretory exacerbations,³ might

also influence disease progression in chronic obstructive pulmonary disease. Exacerbations are important events for patients with chronic bronchitis in that they negatively affect quality of life.¹ Exacerbations also have socio-economic consequences.² Therapies aiming at reducing the occurrence and severity of exacerbations are therefore of interest.

The Cochrane review in this week's issue of the *BMJ* reports a meta-analysis of drugs considered to have mucolytic effects (p 1271).³ Twenty two studies of 10 drugs were included. Treated patients showed a significant reduction over controls in the number of exacerbations (about 0.5 per 6 months) and number of days each exacerbation lasted. No difference in lung function or in adverse effects was seen.

The studies included in the review used different definitions for an exacerbation of chronic bronchitis. In some the presence of mucopurulent or purulent sputum was an obligatory criterion, while in others it was not. The presence of purulent sputum indicates that bacteria may be an important contributing factor to the exacerbation. Effects in studies with such definitions might suggest that the drug has a protective effect against bacterial colonisation and infection of the bronchi, while that is less clear for studies with other definitions.

The drug contributing most to the beneficial results in this review seems to be acetylcysteine (12 studies). However, the mucolytic activity of acetylcysteine is not well documented in chronic bronchitis,⁴ and after oral administration acetylcysteine cannot be shown in bronchial secretions.⁵ Another possible mechanism might be an antioxidative effect; this has been proposed because acetylcysteine or one of its metabolites, glutathione, is a free thiol. A similar substance with higher levels of free thiols did not, however, have any effect on the number of exacerbations,⁶ making the free thiol hypothesis unlikely.

Acetylcysteine treatment has been reported to be negatively related to intrabronchial bacterial presence in patients with chronic bronchitis,⁷ possibly because it reduces the ability of bacteria to adhere to epithelial cells.⁸ Oral therapy might thus theoretically reduce the presence of pathogens in the oropharyngeal cavity, the reservoir for bronchial bacterial colonisation and infection. Interestingly, however, application of α streptococci to the oropharynx after antibiotic therapy in children with repeated episodes of otitis led to a reduced rate of relapse.⁹ This indicates that a normal oropharyngeal flora is an important part of the defence against colonisation and infection of adjacent serous membranes. Ambroxol is another drug studied in this meta-analysis for which alternative explanations for its exacerbation-reducing effect can be envisaged. It is, for example, a secretagogue for surfactant, and surfactant contains substances with antibacterial properties.¹⁰ Ambroxol also has antioxidative properties.¹¹ There is therefore reason to doubt that the exacerbation-reducing effect of the drugs included in this meta-analysis is due to their mucolytic effects.

The clinical use of acetylcysteine in patients with chronic bronchitis and chronic obstructive pulmonary disease varies throughout Europe, probably because of different interpretations of single studies. This systematic review—with its overall finding of a protective effect

on exacerbations—is therefore important. Because bacterial infection is an important cause of exacerbations in chronic bronchitis, antibiotic therapy has been the mainstay of therapy. This week's review, however, suggests that we should pay more attention to preventing exacerbations. Interestingly, other prophylactic measures have also been evaluated recently.

Orally administered bacterial lysates that stimulate immune defence have been used in southern Europe for several years. OM 85 BV, a lysate of eight pulmonary pathogens, has also been evaluated in a meta-analysis, which showed a reduction in exacerbations by 0.6 per 6 months.¹² A large and important study published recently also showed a reduction in hospital admissions in patients with chronic obstructive pulmonary disease after treatment with OM 85 BV.¹³ An oral "vaccine" of whole killed bacteria of non-typeable *Haemophilus influenzae* was evaluated in a recent Cochrane review of six clinical studies.¹⁴ The reviewers conclude that treatment in the autumn reduces the number and the severity of exacerbations of chronic bronchitis. Interestingly these therapeutic possibilities have provoked almost no interest in Scandinavian countries, possibly because none of the research has been performed in Scandinavia.

The present Cochrane report, together with that on oral vaccination with whole killed *Haemophilus influenzae* and the meta-analysis of treatment with OM 85 BV, indicates that different therapeutic regimes might be valuable in preventing exacerbations in chronic bronchitis and chronic obstructive pulmonary disease. This is interesting clinically as prophylaxis may be cost effective.¹² It is also of great theoretical interest and should stimulate studies on possible mechanisms, effects on health related quality of life, and prognosis.

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1 Fletcher C, Peto R. The natural history of chronic airflow obstruction. *BMJ* 1977;i:1645-8.

2 Vestbo J, Prescott E, Lange P. Association of chronic mucus hypersecretion with FEV1 decline and chronic obstructive pulmonary disease morbidity. Copenhagen City Heart Study Group. *Am J Respir Crit Care Med* 1996;153:1530-5.

3 Poole PJ, Black PN. Oral mucolytic drugs for exacerbations of chronic obstructive pulmonary disease: systematic review. *BMJ* 2001;322:1271-4.

4 Houtmeyers E, Gosselink R, Gayan-Ramirez G, Decramer M. Effects of drugs on mucus clearance. *Eur Respir J* 1999;14:452-67.

5 Bridgeman MME, Marsden M, MacNee W, Flenley DC, Ryle AP. Cysteine and glutathione concentrations in plasma and bronchoalveolar lavage fluid after treatment with N-acetylcysteine. *Thorax* 1991;46:39-42.

6 Ekberg-Jansson A, Larson M, MacNee W, Tunek A, Wahlgren L, Wouters EFM, et al. N-isobutylcysteine, a donor of systematic thiols, does not reduce the exacerbation rate in chronic bronchitis. *Eur Respir J* 1999;13:829-34.

7 Riise G, Larsson S, Larsson P, Jeansson S, Andersson B. The intrabronchial microbial flora in chronic bronchitis patients: a target for N-acetylcysteine therapy? *Eur Respir J* 1994;7:94-101.

8 Riise G, Qvarfordt I, Larsson S, Eliasson V, Andersson B. Inhibitory effect of N-Acetylcysteine on adherence of streptococcus pneumoniae and haemophilus influenzae to human oropharyngeal cells in vitro. *Respiration* 2000;67:552-8.

9 Roos K, Håkansson EG, Holm S. Effect of recolonisation with "interfering" alpha streptococci on recurrences of acute and secretory

- otitis media in children: randomized placebo controlled trial. *BMJ* 2001;322:210.
- 10 Wang Y, Griffiths WJ, Curstedt T, Johansson J. Porcine pulmonary surfactant preparations contain the antibacterial peptide prophenin and a C-terminal 18 residue fragment thereof. *FEBS Lett* 1999;460:257-62.
- 11 Nowak D, Antczak A, Krol M, Bialasiewicz P, Pietras T. Antioxidant properties of ambroxol. *Free Radic Biol Med* 1994;16:517-22.
- 12 Bergemann R, Brandt A, Zoellner U, Donner CF. Preventive treatment of chronic bronchitis: a meta-analysis of clinical trials with a bacterial extract

- (OM-85BV) and a cost effectiveness analysis. *Monaldi Arch Chest Dis* 1994;49:302-7.
- 13 Collet J-P, Shapiro S, Ernst P, Renzi P, Ducruet T, Robinson A. Effects of an immunostimulating agent on acute exacerbations and hospitalisations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;156:1719-24.
- 14 Foxwell AR, Cripps AWC. Haemophilus influenzae oral vaccination for preventing acute exacerbations of chronic bronchitis (Cochrane Review). *Cochrane Library* 2000;4.

Safer discharge from intensive care to hospital wards

Randomisation is necessary to disentangle intrinsic patient risk from effects of care

Papers p 1274

Intensive care in the United Kingdom is certainly underprovided relative to many developed countries. The United States spends over 1% of its gross national product on providing intensive care, while Britain spends around 0.05%—possibly twentyfold less.¹ But intensive care remains largely outside the evidence based paradigm—apparently for ethical reasons. Judging the appropriateness of intensive care provision still depends solely on apparent unmet need and observed associations of prognostic indicators with mortality. This week's *BMJ* sees another such study.²

It seems too easy to claim benefit in intensive care on the basis of biological plausibility and observational comparison alone. For example, a recent Cochrane overview of 30 trials on the effect of intravenous albumin for acute renal failure,³ which showed significant harm, was dismissed by some enthusiasts.⁴ The writings of respected and dispassionate authors who have held intensive care to be immune from randomisation do not help this apparent impasse.⁵⁻⁶ In the absence of any rigorous measurement of attributable effect, intensive care will continue to be provided on the basis of evidence that is unacceptable in other areas of health enhancement. With 21st century medical technology this is particularly unfortunate.

The acute physiology score (APACHE) developed by Knaus and others⁷ was designed to provide reliable, physiology based, indices of likely benefit by predicting hospital mortality from measurements made among critically ill adults in hospital. This score has been shown to be a potent measure of casemix that predicts mortality well in the British context⁸ and hence enables comparisons of intensive care performance to be disentangled somewhat from practice variations, be they discretionary or enforced by shortage. Obviously cases that are refused admission to intensive care units cannot be readily compared, since scoring is impossible unless a patient is admitted.⁹ In this week's *BMJ* another score is proposed, which again predicts hospital mortality based on physiological measurements (p 1274).²

Daly et al looked at some 13 000 intensive care patients in 20 centres and derived a score based on physiological and other measurements on the last day in intensive care to predict risk of death before hospital discharge. The objective of the work is to provide intensivists with an index predicting risk of hospital death associated with discharge, so that patients may be discharged sensibly from scarce intensive care unit beds to make room for severely ill patients. The authors also use it to identify extra capacity needed in intensive care units to avoid the discharge of high risk

patients. The main outcome of interest should not, of course, be mortality: it should also include a measure of survival duration and also be quality adjusted.

The measure was derived from a subset of data collected from one of the intensive care units and subsequently tested on a different subset from the same unit and on data from 19 other British centres.² Having derived a score that predicted hospital mortality well on the test data, the authors then used the score to estimate the fate of those discharged while deemed to be at high risk compared with those who were not. Taking patients who were above the risk threshold at some stage during a minimum of a three day stay in the intensive care unit, Daly et al compared the high risk discharged patients with those discharged while at lower risk. The latter had lower actual mortality than the former. The crux of the paper is this comparison, and it is used to predict the consequence of one or two days extra stay in intensive care for high risk patients, when their score would then assign them to the low risk group.

These prognostic indices cannot explain all the intrinsic determinants of mortality in a dynamic system on any absolute scale, whatever the amount of discrimination shown, and sadly the shortfall cannot even be guessed at. Disentangling intrinsic patient risk from effects of care will remain impossible without randomisation. Such evidence about the risk of unnecessary death can be seriously misleading if intensive care is going to have to be assessed in this way. For example providing more intensive care beds in response to refused admissions to intensive care seems to lead, because of consequent changes in the threshold for referral and admission, to a greater total number of refusals¹⁰—and thus, logically, to still more beds.

Similarly here the logic of these extrapolations seems to assume that all clinical decisions in intensive care units are made on the basis of intrinsic need, independently of extrinsic influence, in a static system of patient care. It assumes that experienced clinicians do not assess risk and possible benefit very well in individual patients—which could give rise to some of the observed differences. Assuming that the dominant determinant of actual risk of hospital death is a physiological risk score, however discriminatory, is unwise. Who knows what complex processes led to discharge in each case, and how they might change under different influences on the individual clinical decision. The effect of high dependency beds, to name but one factor, is unassessed by this work.

We need to understand more about the determinants of death in critically ill patients because many