Saturday 15 August 1998

BMJ

Candidate vaccines for Epstein-Barr virus

Several promising approaches for vaccines against primary infection

Owing to our increased understanding of the immune variables that control Epstein-Barr virus infection, detailed planning can now be given to developing a vaccine.[1 2] Commercial and scientific considerations are likely to focus on a vaccine directed towards minimising the clinical consequences of primary infection with Epstein-Barr virus (infectious mononucleosis and post-transplant lymphoproliferative disease) rather than towards malignancies associated with the virus (such as Hodgkin's disease, nasopharyngeal carcinoma, and Burkitt's lymphoma). Several trials are now under way with candidate vaccines against primary infection.

It might be argued that Epstein-Barr virus has evolved to generate an asymptomatic seroconversion as clinical symptoms of infectious mononucleosis are rare in developing countries, where primary infection typically occurs in the first few years of life. In contrast, in Western communities primary infection is delayed until adolescence in 10-20% of individuals, and after infection about half of these will develop infectious mononucleosis, the symptoms of which include pharyngitis, fever, and cervical lymphadenopathy. These observations are important in developing strategies for vaccination against Epstein-Barr virus since they suggest that a vaccine generating a minimal immune response might limit the clinical symptoms of infectious mononucleosis.

Given the potential oncogenicity of Epstein-Barr virus, it is generally assumed that an attenuated virus vaccine would not meet the stringent licensing requirements for a vaccine administered prophylactically to healthy adolescents. This consideration has resulted in the adoption of two separate approaches, both based on subunit vaccines.

The first seeks to exploit the major envelope glycoprotein of the virus, gp340.[3] Impetus for this approach arose from the observation that this protein includes the major neutralising determinants of the virus and that various gp340-based vaccines protect cottontop tamarins from lymphoproliferative disease induced by Epstein-Barr virus.[4 5] Indeed, a clinical trial in China showed that a proportion (6/9) children negative for Epstein-Barr virus who were given recombinant vaccinia virus encoding gp340 gained protection from subsequent infection.[6]

This important observation suggests that neutralising or cell mediated determinants within gp340 might induce sterile immunity against Epstein-Barr virus infection. Despite this promising result, a delivery system using live recombinant vaccinia virus is unlikely to find application as a vaccine against infectious mononucleosis. Nevertheless, SmithKline Beecham in association with Aviron, has announced its intention to initiate a phase I randomised, double-blind clinical trial with a single adjuvanted surface antigen responsible for most of the neutralising antibodies stimulated by Epstein-Barr virus infection.[3 7]

An alternative strategy for a vaccine against infectious mononucleosis is based on the induction of cytotoxic T cells specific to Epstein-Barr virus.[1 2] This approach relies on reducing the clinical symptoms of infectious mononucleosis rather than preventing primary infection. The importance of cytotoxic T cells in controlling disease associated with Epstein-Barr virus has been shown in the case of bone marrow derived post-transplant lymphoproliferative disease, where the lymphomas were successfully resolved by adoptive transfer of uncloned cytotoxic T cell lines stimulated by Epstein-Barr virus cultured in vitro.[8]

This established the important principle that specific cytotoxic T cells are capable of recognising these Epstein-Barr virus-infected B cell expansions in vivo (which also occur in infectious mononucleosis) and gave impetus to efforts to design a vaccine based on cytotoxic T cells. Indeed, the early recipients of an Epstein-Barr virus vaccine might well be Epstein-Barr virus seronegative graft recipients who are at risk of developing post-transplant lymphoproliferative disease.[9] Currently, a phase I clinical trial designed to determine the safety and immunogenicity of Epstein-Barr virus cytotoxic T cell epitope vaccines is in progress in our institute. Healthy volunteers negative for Epstein-Barr virus and who are HLA B8 have been vaccinated with a formulation consisting of a synthetic peptide, FLRGRAYGL (an HLA B8 restricted epitope from Epstein-Barr virus nuclear antigen 3), and tetanus toxoid emulsified in the water in oil adjuvant Montanide ISA 720.[2] To date the vaccine has been well tolerated with no significant adverse reactions.

Since each HLA class I allele presents a different epitope and there is a diversity of HLA alleles in the human population, multiple cytotoxic T cell epitopes will need to be delivered. One approach is to formulate a cocktail of defined epitopes in a single vaccine. Of the current Epstein-Barr virus epitopes identified, five would probably span $>80\%$ of the white population. Another approach might be to make use of a recent technical advance in which multiple, minimal cytotoxic T cells epitopes were genetically conjoined so that the

BMJ 1998;317:423–4

vaccine codes for a synthetic polyepitope protein.[10] Such a "polytope" vaccine will, however, need to be delivered using a vector or naked DNA based modality.

Epstein-Barr virus vaccines directed against Hodgkin's disease, nasopharyngeal carcinoma, and Burkitt's lymphoma are conceptually distinct from those directed against infectious mononucleosis. In general, these tumours have evoked a variety of escape mechanisms enabling them to expand despite an existing Epstein-Barr virus specific response which primarily controls the lifelong latent infection in B lymphocytes.[1] The most potent of these mechanisms is likely to be down regulated Epstein-Barr virus antigen expression. Immunological strategies against these malignancies are thus likely to be therapeutic and could exploit the presence of Epstein-Barr virus in the tumour cells or could focus on tumour antigens not encoded by Epstein-Barr virus.

D J Moss *Senior principal research fellow*
A Suhrbier *Senior research fellow*
S L Elliott *Senior research officer*

Epstein-Barr virus Unit, Queensland Institute of Medical Research, Brisbane, Australia 4029

1 Rickinson AB, Moss DJ. Human cytotoxic T lymphocyte responses to Epstein-Barr virus infection. *Ann Rev Immunol* 1997;15:405-31.
2 Moss DJ, Schmidt C, Elliott SL, Suhrbier A, Burrows SR, Khanna R. Strategies involved in developing an effective vaccine for EBV-associated diseases. *Adv Cancer Res* 1996;69:213-44.
3 Anonymous. Epstein-Barr virus vaccine - Phase 1. *Adis LMS R&D Profiles-vaccines* 1996; Quarter 1:48-9.
4 Morgan AJ. Epstein-Barr virus vaccines. *Vaccine* 1992;10:563-70.
5 Mackett M, Cox C, Pepper SD, Lees JF, Naylor BA, Wedderburn N, et al. Immunisation of common marmosets with vaccinia virus expressing Epstein-Barr virus (EBV) gp340 and challenge with EBV. *J Med Virol* 1996;50:263-71.
6 Gu SY, Huang TM, Ruan L, Miao YH, Lu H, Chu CM, et al. First EBV vaccine trial in humans using recombinant vaccinia virus expressing the major membrane antigen. *Dev Biol Stand* 1995;84:171-7.
7 Bluth J, Garrett P. Aviron announces commencement of Phase I clinical trial of Epstein-Barr virus vaccine. www.aviron.com/press/120397.html 1997;1-2.
8 Rooney CM, Smith CA, Ng CYC, Loftin S, Li C, Krance RA, et al. Use of gene-modified virus specific T lymphocytes to control Epstein-Barr virus related lymphoproliferation. *Lancet* 1995;345:9-13.
9 Thomas JA, Allday MJ, Crawford DH. Epstein-Barr virus-associated lymphoproliferative disorders in immunocompromised individuals. *Adv Cancer Res* 1991;57:329-80.
10 Thomson SA, Sherritt MA, Medveczky J, Elliott SL, Moss DJ, Fernando GJP, et al. Delivery of multiple CD8 cytotoxic T cell epitopes by DNA vaccination. *J Immunol* 1998;160:1717-23.

HIV and hepatitis C among injecting drug users

Success in preventing HIV has not been mirrored for hepatitis C

Injecting drug users have been capable of reducing their risky behaviour in the face of the HIV-AIDS epidemic.[1] To many this risk reduction, shown in numerous studies from different parts of the world, was unexpected as drug users are often regarded as self destructive. Nevertheless, because of the decrease in risky behaviour, the incidence of HIV infection among drug users in most industrialised countries has declined over the years. Thus, in this issue, van Beek et al report that among young injecting drug users in Sydney the incidence of HIV infection in 1992-5 was only 0.2 per 100 person years (p 433).[2] Not so good is their finding that the incidence of infection with hepatitis C virus (HCV) was extremely high: 21 per 100 person years; among those aged under 20 the rate was 76 per 100 person years. Other groups from different countries have also reported a continuing high prevalence and incidence of hepatitis C virus among injecting drug users,[3] though not as high as in this study; this may be to do with the young age of the Australian group.

The low incidence (and prevalence) of HIV among injecting drug users in Australia may be ascribed to that country's public health approach, with wide implementation of preventive measures including needle and syringe exchange programmes. But how can we explain the discrepancy between the low incidence of HIV infection and the high incidence of hepatitis C? One reason is the difference in prevalence between the two viral infections. The prevalence of HIV in the Australian group was 2.5% while that of hepatitis C virus was 45%. So, if in that environment an injecting drug user shares injecting equipment with someone else the chance that this equipment is infected with hepatitis C virus is considerably greater than for HIV.

But this is not the only explanation. Hepatitis C virus is much more efficiently transmitted through blood than HIV infection—for sexual transmission it is the other way around. The rate of hepatitis C virus antibody seroconversion among healthcare workers in Japan who had been exposed through needlestick injuries to blood from patients positive for hepatitis C virus was 3-9%.[3] This is more than 10 times higher than the 0.3% HIV seroconversion rate after needlestick incidents with HIV positive patients.[4] The high transmission efficiency of hepatitis C virus may also explain its transmission in drug users in the Australian study who did not report a history of sharing equipment. This could have been due to indirect sharing—that is, sharing of injecting accessories such as spoons and cotton—or to front and back loading—dividing drugs by sticking the needle of one syringe into another (used) syringe—which is often not seen as sharing by drug users.

The clinical consequences of hepatitis C virus infection are serious, especially in the long term.[5] Although most acute hepatitis C infections are subclinical, in 80-85% of cases the infection persists and usually leads to chronic hepatitis, which can result in cirrhosis and rarely hepatocellular carcinoma. The mean period between infection with the virus and its consequences is long: about 20 years for cirrhosis and 29 years for hepatocellular carcinoma. There is no convincing evidence that the progression to cirrhosis is influenced by drug use itself, but other risk factors like coinfection with hepatitis B and HIV and hepatotoxic agents like alcohol enhance progression. As these risk factors are common among injecting drug users, their incubation period between infection and its sequelae

Papers p 433

BMJ 1998;317:424–5

may be shorter. On the other hand, mortality among injecting drug users is high: a study among injecting drug users in the Netherlands showed 1.8 deaths per 100 person years in those who were HIV negative and 6.4 per 100 person years in those who were HIV positive.[6] Therefore, some drug users with hepatitis C virus will not survive long enough to develop cirrhosis or carcinoma.

Because of its long term consequences hepatitis C virus infection should be treated, although the sustained response rate after treatment (currently with interferon, preferably in combination with ribavirin) is only 20-30%.[7] Other drugs for treating the infection are being developed and may have better results.

What can we do about the hepatitis C virus epidemic in injecting drug users? It is clearly an extra reason to strengthen programmes aimed at reducing sharing of injecting equipment by drug users. However, many industrialised countries have, like Australia, already implemented such programmes and there seems to be only limited room for improvement. More attention could be paid to preventing indirect sharing, as this may be an important transmission route for hepatitis C virus. And peer education—which has been shown to be very effective among homosexual men—is an option that has not been sufficiently explored among injecting drug users. But we have to remain realistic. The residual risk among injecting drug users will be hard to prevent, especially as part of this behaviour appears to be deliberate (unpublished data). In the Netherlands stopping injecting ("the switch") was recently the topic of a national campaign implemented by an organisation with close links to injecting drug users. Another approach is to try to prevent drug users from starting injecting. And, of course, the best option is not to use drugs at all.

We have been reasonably successful in stemming (but not stopping) the HIV epidemic among injection drug users. The Australian data show that we have not been at all successful in stemming the spread of hepatitis C virus.

R A Coutinho *Director and professor of epidemiology and control of infectious diseases*

Division of Public Health and Environment, Municipal Health Service, 1018 WT Amsterdam, Netherlands

1 Van Ameijden EJC, Watters JK, van den Hoek JAR, Coutinho RA. Interventions among injection drug users: do they work?. *AIDS* 1995;9(suppl A):S75-84.
2 Van Beek I, Dwyer R, Dore GJ. Infection with HIV and hepatitis C virus among injecting drug users in a prevention setting: retrospective cohort study. *BMJ* 1998;317:433-7.
3 MacDonald M, Crofts N, Kaldor J. Transmission of hepatitis C virus: rates, routes and cofactors. *Epidemiologic Reviews* 1996;18:137-48.
4 Tokars JI, Marcus R, Culver DH, Schable CA. McKibben PS. Bandea CI, et al. Surveillance of HIV infection and zidovudine use among health care workers after occupational exposure to HIV-infected blood. *Ann Intern Med* 1993:118:913-9.
5 Van der Poel CL, Cuypers HT, Reesink HW. Hepatitis C virus six years on. *Lancet* 1994;344:1475-9.
6 Van Haastrecht HJA, van Ameijden EJC, van den Hoek JAR, Mientjes GHC, Bax JS, Coutinho RA. Predictors of mortality in the Amsterdam Cohort of HIV-positive and HIV-negative drug users. *Am J Epidemiol* 1996;143:382-91.
7 Reichard O, Norkrans G, Frydén A, Braconier J-H, Sönnerborg A, Weiland O for the Swedish Study Group. Randomised, double-blind, placebo-controlled trial of interferon α-2b with and without ribavirin for chronic hepatitis C. *Lancet* 1998;351:83-7.

Cholesterol: how low is low enough?

Reaching target levels may be better than relative reductions

Not so very long ago many of us did not realise the importance of cholesterol lowering in patients with coronary disease. After the World Health Organisation's clofibrate trial[1] many patients with hyperlipidaemia, with or without manifest coronary disease, were left without cholesterol lowering treatment. Now, after several large placebo controlled trials, the message is clear: patients with coronary disease and high or normal serum cholesterol concentrations benefit from cholesterol lowering treatment, by a 20-40% reduction in coronary events.[2,3] What remains less clear is by how much to lower those concentrations and whether it is the absolute concentration or the percentage reduction that matters most.

Current guidelines recommend a treatment goal for low density lipoprotein cholesterol of 2.6 mmol/l in patients with coronary disease.[4,5] However, statins, the most widely used drugs for cholesterol lowering, reduce cholesterol values not to a specific level but in proportion to pretreatment values. Thus the absolute reduction in concentration will be greater in patients with high initial values, but in these patients the target value will also be harder to achieve. Furthermore, angiographic trials have shown that percentage changes in stenoses are significantly correlated not with the achieved concentration of low density lipoprotein cholesterol but with its percentage reduction.[6] Some have suggested that it may be more practicable to recommend the percentage by which low density lipoprotein cholesterol concentrations should be lowered rather than setting target levels.[5]

Lower serum cholesterol concentrations are associated with lower risk of coronary disease throughout the range considered normal in Western populations. This is a dynamic process: as population levels of serum cholesterol decrease, as a result of dietary changes, so does mortality from ischaemic heart disease.[7] Data from a Chinese population show that the positive relation between coronary risk and serum cholesterol concentration continues down to values well below the range of Western populations, with no evidence of a threshold effect.[8] In observational studies a prolonged difference in usual serum cholesterol value of 0.6 mmol/l is associated with an almost 30% reduction in risk of coronary disease.[9] The effects of a similar difference in the randomised controlled trials of statins are smaller, possibly because the trials did not extend beyond five years. More prolonged cholesterol lowering may result in greater reductions in risk.

BMJ 1998;317:425–6

Data derived from several sources show a log linear relation between low density lipoprotein cholesterol concentration and risk of coronary disease.[5] As the absolute reduction in low density lipoprotein cholesterol induced by cholesterol lowering drugs will be larger with higher initial levels and, as the relation between low density lipoprotein cholesterol and risk of coronary disease is curvilinear, this larger reduction will result in a proportionately greater net reduction in coronary events. In terms of reduction in absolute risk in a particular individual, the reduction will be determined as much by his or her overall coronary risk, as by the initial cholesterol concentration. The presence of coronary disease means a higher absolute risk and that the same net benefit in terms of reduced coronary events can be expected at lower initial lipid levels in patients with established coronary disease.

So far, clinically important reductions have been achieved only in patients at high risk. Both the Scandinavian Simvastatin Survival Study (4S) and the Cholesterol and Recurrent Events (CARE) study show, furthermore, that the proportional reduction in risk is similar, irrespective of the initial cholesterol concentration, except for those in the CARE study with baseline low density lipoprotein values below 3.2 mmol/l. It is unknown whether lowering of low density lipoprotein cholesterol to values below those achieved by the 4S study or the CARE study will reduce coronary events further. Extrapolation from observational and randomised controlled studies, however, suggests that achievement of lower low density lipoprotein concentration in patients with coronary disease with high or normal cholesterol values may reduce coronary events by perhaps as much as 15-20%.

Is this effort worthwhile? In the absence of evidence from trials of more intensive cholesterol lowering this is, so far, conjectural. However, considerable scope exists for attempting to improve the prognosis of patients with coronary disease. In the study population of the 4S trial the risk of coronary death in the treated group at 5.4 years was still 5%. This should be compared with the risk of 1.7% during 4.9 years' follow up in the placebo group in a primary prevention trial of pravastatin in men with hypercholesterolaemia but no prior infarction.[10] Consequently, a further reduction in risk in a population at high risk could lead to a not unimportant number of lives saved. Whether the additional numbers needed to be treated are justified by the number of coronary events saved is not clear, nor is whether prolonged intensive cholesterol lowering by medication will lead to excess non-coronary mortality. Also there are probably many patients at high risk who are not being treated at all. Nevertheless, to the best of our current knowledge, settling for proportional lowering of serum cholesterol values, instead of attempting to achieve target levels, will mean less than optimal treatment in a fair share of patients with coronary disease.

A Rosengren *Associate professor*

Section of Preventive Cardiology, Department of Medicine, Sahlgrenska University Hospital/Östra, S-416 85 Göteborg, Sweden

1 Committee of Principal Investigators. WHO co-operative trial on primary prevention of ischaemic heart disease using clofibrate to lower serum cholesterol: mortality follow-up. *Lancet* 1980;ii:379-85.
2 Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.
3 Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole CG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001-9.
4 Management of stable angina pectoris. Recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J* 1997;18:394-413.
5 Cullen P, Assmann G. Treatment goals for low-density lipoprotein cholesterol in the secondary prevention of coronary heart disease: absolute levels or extent of lowering? *Am J Cardiol* 1997;80:1287-94.
6 Thompson GR, Hollyer J, Waters DD. Percentage change rather than plasma level of LDL-cholesterol determines therapeutic response in coronary heart disease. *Curr Opin Lipidol* 1995;6:386-8.
7 Vartiainen E, Puska P, Pekkanen J, Tuomilehto J, Jousilahti P. Changes in risk factors explain changes in mortality from ischemic heart disease in Finland. *BMJ* 1994;309:23-7.
8 Chen Z, Peto R, Collins R, MacMahon S, Lu J, Li W. Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. *BMJ* 1991;303:276-82.
9 Law MR, Wald NJ, Wu T, Hackshaw A, Bailey A. Systematic underestimation of association between serum cholesterol concentration and ischaemic heart disease in observational studies: data from the BUPA study. *BMJ* 1994;308:363-6.
10 Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-7.

Disease management in Europe

Likely to grow as pressure to deliver cost effective care mounts

Can healthcare providers improve the cost effectiveness of patient care by contracting out chunks to pharmaceutical companies? The evidence is equivocal, but the experiment is under way as drug companies move into chronic disease management.

The theory is as follows. Systematic, integrated, evidence based, long term care of populations of patients with chronic, high cost diseases such as asthma, back pain, rheumatoid arthritis, dementia, and diabetes is more effective than episodic fragmented care of individuals. The incidence of acute episodes and complications associated with disease is reduced and quality of life improves.[1] Better health outcomes reduce costs. Setting up "disease management" programmes that operate across the boundaries of primary, secondary, and community care requires high capital investment and state of the art information technology. Few health care providers can readily supply these. Pharmaceutical industries can. Hence the logic of contracting out services or setting up joint ventures.

The difference between shared care (as, for example, in diabetes and asthma in Britain), and disease management is essentially one of quality—and control. Commercial programmes are built on rigorous economic as well as medical knowledge of the entire course of disease. There is huge emphasis on efficient delivery systems, tight monitoring, continuing

BMJ 1998;317:426–7

audit and quality assurance, prevention, patient education, and the use of continually refined protocols and guidelines. The staff employed to run the programmes are given intensive and continuing training and support.[2]

In the past 10 years pharmaceutical companies in the United States and to a lesser extent in Europe have established various programmes. Many are for diabetic care but others include prenatal care, palliative care, management of end stage renal disease, and the care of patients with stroke. Programmes vary in size and scale, but several operate internationally and provide full services and products for each phase of care in a given disease.

The extent to which Europe will follow the United States down this commercial route was recently debated by the European Health Policy Forum. Much depends on individual countries' healthcare systems. The scope for improving standards and reducing costs through disease management programmes is largest in countries such as Germany and Belgium where primary care is comparatively weak and the healthcare market is competitive, unregulated, and costly.

One approach advocated is for providers to adopt the principles and practice of commercial disease management while remaining independent. The problem here is persuading health ministers that the investment in information technology and infrastructure is cost effective.[3] This is not easy given that few data exist on the effect of disease management on overall healthcare costs. Nevertheless, experience does suggest that, as well as improving disease control, these programmes are liked by patients and staff. One reason, according to Professor Cor Spreeuwenberg, director of primary health care studies, Maastricht University, may be that nurses assume the major role in provision of care. "Patients like seeing them and they tend to follow protocols better than doctors."

The fact that a third of European drug companies have, or are developing, disease management programmes suggests that industry at least sees a future in them. Start up costs are high but judged worthwhile in return for credibility and market advantage. Where collaborative ventures are set up with reputable provider units the prestige for the company is considerable. There is also a guaranteed market for products and the opportunity to collect valuable long term outcome data on unselected patient populations.

"In the next few years we will see many more partnerships," said Dr Johan Matthijs of Hoechst Marion Rousell, "not only between doctors and industry but between industry and governments too. One key factor that will determine the growth of disease management is how budgets are allocated. If they are set on a per capita basis the incentive is low, but when they are allocated per disease group the incentive rises rapidly. Another factor is the quality of information technology. These programmes require a common electronic record and fully computerised decision support and quality control systems."

As experience of disease management grows, more attention is being focused on the possible disadvantages. Medical "carve outs" that entail patients being directed to specialist units for one disease risk fragmentation of care, especially for patients with multiple unrelated pathology.[4] Concern has been expressed that disease management is more of a marketing tool for the drug industry than an efficient way of delivering care.[5] The jury is still out over whether reduced costs are sustained long term. Real concern also exists over whether professional independence can be guaranteed in commercially driven enterprises.

Nevertheless, the pressure on governments to contain costs and foster evidence based, effective medical care is likely to encourage entrepreneurial collaboration between the health care sector and industry. Adoption and adaptation of its skills and technology may offer much.[6] Providing that collaboration is fully transparent, patients seem unlikely to lose.

Tessa Richards *Associate editor, BMJ*
(tessarichards@compuserve.com)

1 The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993;329:977-86.
2 Hunter DJ, Fairfield G. Disease management *BMJ* 1997;315:50-3.
3 Lawrence M, Williams T. Managed care and disease management in the NHS. *BMJ* 1996;313:125-6.
4 Steinbrook R. Patients with multiple chronic conditions: how many medications are enough? *N Engl J Med* 1998;338:1541-2.
5 Harris JM. Disease management: new wine in new bottles? *Ann Intern Med* 1996;124:838-42.
6 Garibaldi RA. Computers and the quality of care: a clinician's perspective. *N Engl J Med* 1998;338:259-6.

Guidelines for clinical guidelines

A simple, pragmatic strategy for guideline development

Clinical guidelines are systematically developed statements designed to help practitioners and patients make decisions about appropriate health care for specific circumstances.[1] Clinicians are being inundated by a tidal wave of guidelines. In Britain alone, regional programmes for audit have recently developed about 2000 guidelines or protocols.[2] In addition to numerous clinical guidelines, a number of "guidelines for guidelines" have been produced, ranging from simple[3] to complex.[4] These reflect the increasing attention being paid to the methodology of guidelines development and the validity of guideline recommendations. While we support the increasingly rigorous approach taken to guideline development, it is important to re-emphasise the central role of guidelines themselves, which is to help clinicians make better decisions.

Clinicians need simple, patient specific, user friendly guidelines. We highlight three key components for such guidelines. The first is the explicit identi-

BMJ 1998;317:427–8

fication of the major decisions, relevant to patients, which have to be made, and the possible consequences of these decisions. Many encounters with patients involve multiple decisions, so the key to developing usable guidelines is to identify only the most important ones. These decisions and their consequences may often be difficult to map, and remarkably little is known about how doctors actually make decisions.[5] But unless we limit guidelines to the major decision points, they are likely to be too unwieldy to use in practice.

The key clinical decisions generally relate to making a diagnosis; estimating prognosis; assessing relevant outcomes, including the benefits, risks, and costs of alternative treatments; and, finally, weighing up the various consequences of different treatment options. It should be possible to produce a flow diagram or algorithm which identifies the key decisions and important outcomes relevant to patients and others.

The second component of successful guidelines involves bringing together the relevant, valid evidence that clinicians need to make informed decisions at each of the key decision points. This remains the most difficult step as, in many if not most clinical areas, the necessary research evidence is inadequate, and methodologists continue to struggle with these shortcomings. The increasing interest in evidence based practice and guidelines has highlighted the huge gaps in the evidence, although recent studies suggest that the potential to make evidence based decisions may be greater than generally believed.[6] Moreover, groups such as the Cochrane Collaboration, the York Centre for Reviews and Dissemination, and the United States Agency for Health Care Policy and Research, will increasingly be able to provide guideline developers with comprehensive and systematic overviews of the evidence.

One of the cornerstones of evidence based practice (and evidence based clinical guidelines) is the requirement that the evidence is relevant to individual patients.[7] Much of the evidence presented in formal overviews, although comprehensive and valid, is not in a form directly relevant to individual patient care. For example, overviews typically summarise treatment effects in terms of relative risks or benefits, whereas treatment decisions, where possible, should be guided by the absolute risks and benefits of treatment. These measures can be presented in units such as events per 100 patients treated (or untreated) per year, or the number of patients who would need to be treated to prevent an event (number needed to treat).[8] An example can be viewed at the following website: http://cebm.jr2.ox.ac.uk/docs/prognosis.html. As more research on the cost-effectiveness of treatments is published, this too needs to be incorporated in a relevant form into guidelines. The more guidelines can present evidence which can be applied to individual patients, the more useful they will be for real life clinical decision making. Explicit statements about the benefits and risks of treatment can then be weighed by patient preferences and available resources.[9] This is currently difficult to achieve for most clinical problems, making it necessary to write more general guidelines,[10] which are less explicit because the evidence does not allow the calculation of outcome probabilities. None the less, guideline developers should be encouraged to follow the process outlined above and acknowledge where recommendations are based on inadequate evidence.

Key components of a useful clinical guideline

- Identification of the key decisions and their consequences
- Review of the relevant, valid evidence on the benefits, risks, and costs of alternative decisions
- Presentation of the evidence required to inform key decisions in a simple, accessible format that is flexible to stakeholder preferences

A third essential component of a successful guideline is the presentation of evidence and recommendations in a concise, accessible format. Decision makers must be able to retrieve and assimilate information quickly. Moreover, information must be presented in a flexible format that is applicable to specific patients or circumstances. As clinicians move into the computer age, the possibilities of more immediate access to the relevant evidence will increase.

We consider these three components to be basic building blocks of usable clinical guidelines. The embarrassingly wide variation in much healthcare practice suggests clinicians use different information to inform the same decisions. In a significant proportion of clinical situations, guidelines could become the common language enabling patients, practitioners, scientists, and purchasers the opportunity to share information more effectively. However, "guidelines for clinical guidelines" need to be kept simple and need to focus on the essential components of usable guidelines. Unless we can communicate a simple, pragmatic strategy for guideline development, we will continue to be embarrassed by variations in clinical guidelines as we are by inappropriate variation in clinical practice.

Rodney Jackson *Associate professor*

Department of Community Health, School of Medicine, University of Auckland, Private Bag 92019, Auckland, New Zealand

Gene Feder *Senior lecturer*

Dept of General Practice and Primary Care, St. Bartholomew's and The Royal London School of Medicine and Dentistry, Basic Medical Sciences, Mile End Road, London E1 4NS

1 Field MJ, Lohr KN, eds. *Guidelines for clinical practice. From development to use.* Washington, DC: National Academy Press, 1992.
2 Stern M, Brennan S. *Medical audit in the hospital and community health services.* London: Department of Health, 1994.
3 Eddy D. Practice policies: guidelines for methods. *JAMA* 1990;263:1839-41.
4 Eccles M, Clapp Z, Grimshaw J, Adams PC, Higgins B, Purves I, Russell I . North of England evidence based guidelines development project: methods of guideline development. *BMJ* 1996;312:760-2.
5 Denig P, Haaijer-Ruskamp FM. 'Thinking aloud,' as a method of analysing the treatment decisions of physicians. *Eur J Pub Health* 1994;4:55-9.
6 Ellis J, Mulligan I, Rowe J, Sackett DL. Inpatient general medicine is evidence-based. *Lancet* 1995;346:407-10.
7 Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence-based medicine: what it is and what it isn't. *BMJ* 1996;312:71-2.
8 Jackson R, Sackett D. Guidelines for managing raised blood pressure: evidence-based or evidence-burdened? *BMJ* 1996;313:64-5.
9 Dowie J. 'Evidence-based', 'cost-effective' and 'preference-driven' medicine: decision analysis based medical decision making is the pre-requisite. *J Health Serv Res Policy* 1996; 1:104-13.
10 Feder G. Clinical guidelines in 1994. Let's be careful out there. *BMJ* 1994;309:1457-8.