Short cuts

What's new in the other general journals

Mild gestational diabetes should be treated

Clinicians have been waiting a long time for some decent evidence to help resolve the debate about whether to screen for and treat glucose intolerance during pregnancy. A large trial of 1000 women has found, 12 years after it began, that actively treating women with mild gestational diabetes reduces the risk of serious perinatal complications, including neonatal death, and may even prevent postnatal depression. Women with severe gestational diabetes were excluded from this trial, which compared active treatment (blood glucose monitoring, diet, and insulin if required) with no treatment.

Controversially, the 510 women in the control group were not told that they had gestational diabetes. Their care was designed to replicate the care given to women attending hospitals that do not screen. Four per cent of their babies had a serious perinatal problem defined as death, shoulder dystocia, bone fracture, or nerve palsy. The rate of serious perinatal problems among the treated women was only 1%, a significant difference that translates to one serious complication fewer for every 34 women treated (95% confidence interval 20 to 103) and supports arguments for screening all pregnant women for glucose intolerance. Untreated women were also more likely to have a large baby (21% *v* 10%, $P < 0.001$). Three months after delivery, treated women had lower depression scores and better health related quality of life than control women.

New England Journal of Medicine 2005;352:2477-86

Mechanical reperfusion reduces infarct size in patients who present late after heart attack

We already know that thrombolytic drugs do not work more than 12 hours after a heart attack. Mechanical reperfusion could be a reasonable alternative, according to a recent trial in 365 patients who presented to hospital 12-48 hours after the start of their symptoms. The trial was too small to assess the impact of treatment on survival, but it did find that late presenters who were taken straight to the catheter laboratory for mechanical reperfusion—usually a coronary stent combined with intravenous abciximab—had smaller infarcts five to

10 days later than patients who were managed conservatively (8% *v* 13%, $P < 0.001$). All the patients had had an uncomplicated heart attack with ST elevation but without persisting chest pain, and they were all given an antiplatelet drug and a bolus of heparin.

The authors say these results support the theory that heart muscle remains viable for many hours after ischaemia sets in and that mechanically opening up the affected artery can save at least some of it. It's too early to say if an invasive strategy can save lives too, although we do know that smaller infarcts are associated with a better prognosis than bigger ones.

JAMA 2005;293:2865-72

Orlistat may help obese teenagers lose a little weight

Orlistat is a lipase inhibitor that reduces the absorption of fat and its associated calories. Under the right circumstances orlistat can help obese adults to lose a modest amount of weight, but can it work in adolescents, who are traditionally far more difficult to treat? A randomised trial of 539 obese adolescents has found that those taking orlistat as part of a package including diet and exercise lost more weight over one year than those on the same diet and exercise programme taking placebo. As with adults, the loss was modest. After a year, 26.5% of teenagers taking orlistat and 15.7% of teenagers taking a placebo had reduced their body mass index (kg/m^2) by at least 5% ($P = 0.005$). Also, the orlistat group had reduced their body mass index by 0.55, whereas the placebo group had increased theirs by 0.31 ($P = 0.001$). Gastrointestinal side effects were more common in the orlistat group, but none were serious.

Orlistat is now licensed for teenagers in the United States, thanks partly to the results of this industry sponsored trial, but in an accompanying editorial (pp 2932-4)

a leading commentator said that doctors should not rush to prescribe it. There are still doubts about orlistat's long term safety in young people, who could be struggling with weight loss for many years. It's also hard to tell which component of the treatment package contributed most to participants' weight loss. There's no evidence here that orlistat works on its own.

JAMA 2005;293:2873-83

Using generic drugs would cut 11% off US drugs bill

US doctors could cut nearly \$9bn (£5bn; €7.5bn) off the government's healthcare budget simply by prescribing only generic drugs, a survey has found. Drugs expenditure in the US totalled \$141bn in 2001. The study's authors estimate that a policy of switching from branded to generic products whenever possible would reduce drugs expenditure by about 11% at a time when both private and public payers are fighting to contain costs.

Their study was based on national survey data collected by the Agency for Healthcare Research and Quality, which showed that 56% of all prescriptions dispensed between 1997 and 2000 were for drugs that had branded or generic alternatives. Overall, 61% of these were dispensed as generics, although the use of generics increased slightly over the three years of the study—from 58% to 64%. Switching all branded products to generics would save \$45.89 per person aged under 65 and \$78.05 per person aged 65 or over, a total saving nationwide of \$5.9bn (95% confidence interval \$5.5bn to \$6.2bn) and \$2.9bn (\$2.6bn to \$3.1bn) respectively.

The authors say these substantial savings could be even greater if there was keener competition in the generic market, if the US Food and Drug Administration accelerated their licensing procedures for generics, and if drug companies could be persuaded not to extend patents on "blockbuster" brand named drugs.

Annals of Internal Medicine 2005;142:891-7

Early treatment of epilepsy reduces short term but not long term risk of seizures

People who have one or two well defined epileptic seizures may never have another, so deciding whether to give them

potentially toxic antiepileptic drugs can be very difficult. The latest randomised trial to compare early with deferred treatment, and one of the few long term trials, found that early treatment helped to prevent seizures at first but made no difference to the chance of remission in the long term. Five years after randomisation, about three quarters of participants in both groups had been free of seizures for two years (76% *v* 77%). The early benefits of immediate treatment with antiepileptic drugs were offset by an increase in side effects, and the timing of treatment made no difference to patients' quality of life or ability to work.

The trial included 1443 participants (mainly teenagers and young adults) with a recent history of one or more epileptic seizures. Half of them began treatment immediately, usually with carbamazepine (46%) or valproate (46%). The other half deferred treatment until both patient and doctor decided it was necessary. Overall about half the participants had a seizure during follow-up.

Despite failing to recruit the required 3000 patients, the authors are confident that their study is big enough and conclusive enough to reassure neurologists and their patients that deferring treatment after a first seizure will not increase the risk of chronic epilepsy.

Lancet 2005;365:2007-13

Patients with transient ischaemic attacks and minor strokes still have poor long term prognosis

Clinical trials suggest that about a fifth of patients who have a transient ischaemic attack or stroke will have another one within five years. A recent prognostic study reports that the risks of stroke or death continue to rise for at least the next five years as well. Fewer than half (48%) of the

patients in this study survived event-free for 10 years after a minor stroke or transient ischaemic attack.

The patients, all Dutch, were originally recruited for a randomised trial of antiplatelet therapy. Of the 2473 in total, 2447 were followed up for a mean of 10.1 years. Sixty per cent of them died during that time, and 54% had at least one new vascular event, including vascular death, non-fatal heart attack, and non-fatal stroke. The mean yearly risk of a vascular event, including vascular death, was 5.7%. Patients most likely to die included those older than 65 years (hazard ratio 3.3) and those with diabetes (2.10), claudication (1.77), previous peripheral vascular surgery (1.94), or pathological Q waves on their baseline electrocardiogram (1.5). Prognostic factors for vascular events were similar.

Patients who have a transient ischaemic attack or minor stroke have the same order of immediate and ongoing risks as patients with unstable angina, said one leading commentator (pp 2065-6), and they should be treated with the same urgency and followed up regularly and long term.

Lancet 2005;365:2098-104

Teenager survives rabies without immune prophylaxis

A 15 year old girl has survived rabies after a novel treatment package including ketamine induced coma and antiviral drugs. The girl presented with symptoms of rabies one month after being bitten by a bat, and too late for standard immune prophylaxis with rabies vaccine or rabies immunoglobulin. Doctors at a Milwaukee hospital in the United States anaesthetised her with ketamine, midazolam, and barbiturates, then added ribavirin and amantadine, hoping to keep her alive while her own immune response matured. She developed neutralising antibodies in the second week and was extubated on day 27. She is now back at home, but with fairly severe neurological problems including choreoathetosis, dysarthria, and an unsteady gait.

We still don't know for certain why people die of rabies, but animal studies suggest it might have something to do with autonomic failure and disruption of neurotransmitter function. This improvised treatment package was designed to minimise both and to protect the central nervous system while the girl's own immune system cleared the virus. It may have worked. There are only five other reports of rabies survivors, all of whom had immune prophylaxis either before or after exposure.

It's impossible to say for certain whether this girl survived because of her treatment or in spite of it. But the case should at least provide another lead to

follow in the search for effective weapons against one of the world's deadliest infectious diseases.

New England Journal of Medicine 2005;352:2508-14

Smoking and obesity accelerate ageing in women

Telomeres, which cap the end of chromosomes, get shorter as you get older, making them a reasonable biological marker for ageing. Scientists looking at telomeres in white blood cells in humans have discovered that they get shorter by about 27 base pairs a year and that the ageing process is accelerated by smoking and obesity.

In their study, which included 1122 women from a UK twin registry, smokers had shorter telomeres than former smokers, who in turn had shorter telomeres than non-smokers. Smokers lost an extra five base pairs for each pack year smoked compared with the rest of the cohort, an ageing effect equivalent to 7.4 years for a woman who smokes a pack a day for 40 years. The effects of obesity looked even worse. Obese women had telomeres that were 240 base pairs shorter than telomeres in lean women, adding an estimated 8.8 years to their biological age.

The authors think the ageing effects of smoking and obesity are caused by increased inflammation and oxidative stress to cells. Whatever the mechanism, the prospect of rapid ageing will be a powerful incentive for many women to adopt a healthier lifestyle.

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