Short cuts

What's new in the other general journals

Long term anticoagulation reduces recurrence of venous thromboembolism

Patients who survive an episode of venous thromboembolism are at risk of a recurrence, which is why they are usually treated with warfarin. But how long should this treatment continue? Randomised controlled trials investigating the impact of different durations of anticoagulation have reported conflicting results. A meta-analysis helps to resolve the discrepancies, but there is probably no straightforward answer.

Fifteen randomised controlled trials evaluating different durations of anticoagulation in terms of risk of recurrence were included in the meta-analysis. The investigators found that the discordance between trials that reported large benefits and others that reported only small or no benefit was largely explained by differences in the periods used for defining recurrence rates. Differences in the baseline prevalence of risk factors accounted for much of the variation in event rates between studies.

The investigators conclude that long term anticoagulation in patients with venous thromboembolism does reduce the risk of recurrence. The magnitude of this risk reduction is greatest while the patient is receiving treatment, but even after treatment is stopped there is benefit. The incremental benefit of prolonging anticoagulation decreases as the duration of anticoagulation increases but lasts for at least six months.

JAMA 2005;294:706-15

Pulmonary artery catheters do not reduce mortality in intensive care patients

Pulmonary artery catheters have been used for 30 years to monitor cardiac output and other haemodynamic variables in severely ill patients. Although they are ingenious pieces of technology, argument continues over whether the quality of the information they provide outweighs the complications associated with their insertion. A randomised trial involving over 1000 patients from 65 intensive care units in the UK reports no difference in mortality or length of stay in hospital between patients managed with or without a catheter.

The trial was pragmatic in its approach. Clinicians enrolled patients who they thought should be managed with a pulmonary artery catheter but, after randomisation, other decisions about treatment, including the length of time the catheter remained in place, were left to them. A commentary accompanying the article raises interesting, but unanswerable, questions: were the decisions about treatment the same whether or not a pulmonary artery catheter was in place, or were the decisions different but irrelevant in modifying prognosis? In other words, is it pulmonary artery catheters or the use made of the information they yield that fails to make a difference? If the latter, developing less invasive methods of measuring haemodynamic variables may be of little benefit. Perhaps it's time to pay more attention to non-haemodynamic physiopathological information in critically ill patients.

Lancet 2005;366:472-7

Combination antibiotic susceptibility testing doesn't improve outcomes in cystic fibrosis

Antibiotic resistance is a problem all over the world. People with cystic fibrosis are particularly badly affected, with 25-45% of adults with the disease chronically infected with multiresistant bacteria in their airways. Combination therapy with two antipseudomonal antibiotics is better than monotherapy for treating pulmonary exacerbations. It extends the time to next exacerbation, but it's difficult to know which combination of antibiotics to select when the bacterial organisms are multiresistant to antibiotics on routine sensitivity testing. In recent years, methods for in vitro testing of combinations of double and triple antibiotics for bactericidal activity against multiresistant bacterial isolates have been

devised. Disappointingly, the results of a randomised controlled trial show that, even when these methods are used, outcomes are not improved.

A total of 251 patients with cystic fibrosis who were chronically infected with multiresistant Gram negative bacteria gave sputum at intervals of three months for conventional culture and sensitivity tests and for combination antibiotic susceptibility tests. During the study, 132 of them developed an exacerbation during the study period and were randomised to receive a 14 day course of any two intravenous antibiotics, which were chosen on the basis of the results of either the conventional test or the combination test. The treatment failure rate was the same in the two groups. After 14 days of intravenous antibiotic therapy, changes in lung function, dyspnoea, and sputum bacterial density were similar in both groups. The time to the next pulmonary exacerbation was also the same in the two groups.

The authors speculate that non-bactericidal effects of antibiotic therapy are important in cystic fibrosis. Azithromycin, for example, an antibiotic that has no bactericidal effects against *Pseudomonas aeruginosa*, improves clinical outcomes, perhaps because of its anti-inflammatory effects. Another possibility is that in vitro antibiotic susceptibility is a poor indicator of clinical response.

Lancet 2005;366:463-71

Non-melanoma skin cancer is increasing in young adults

Non-melanoma skin cancer is predominantly a disease of older people and its incidence is known to be rising, probably because of increased cumulative exposure to ultraviolet light. A population based study from the US finds that the

incidence of non-melanoma skin cancer is increasing in younger people too. Using data from the Rochester epidemiology project, the investigators identified incident basal cell carcinomas and squamous cell carcinomas in people under 40, and estimated change in incidence over the period 1976-2003.

In total, they found 451 basal cell carcinomas and 70 squamous cell carcinomas. Most had been confirmed histologically. The incidence of basal cell carcinoma had increased significantly during the study period among women, but not men, whereas the incidence of squamous cell carcinoma increased in both sexes. The age adjusted annual incidence of basal cell carcinoma was 25.9/100 000 for women and 20.9/100 000 for men. The incidence of squamous cell carcinoma was similar for men and women, with an average age adjusted incidence of 3.9/100 000. The authors think it unlikely that the rising incidence can be accounted for by greater public awareness or better surveillance because there was no trend of decreasing size in tumours at diagnosis. They suspect that it's the result of sunbathing and the use of tanning parlours. *JAMA* 2005;294:681-90

Alendronate prolongs the effects of parathyroid hormone on bone

Osteoporosis can be treated with drugs in two ways. One is to use anabolic agents such as human parathyroid hormone to stimulate bone formation; the other is to use drugs such as bisphosphonates to reduce bone resorption. How best to combine these approaches is becoming clearer with the results of two new trials carried out in postmenopausal women with osteoporosis.

In the first, initially a three armed trial that compared monotherapy with either parathyroid hormone or the bisphosphonate, alendronate (alendronic acid) against combination therapy with both agents, those assigned to parathyroid hormone monotherapy were randomly allocated to one additional year with either placebo or alendronate. Participants who had first received combination therapy

were given alendronate in the second year, whereas those who had received alendronate monotherapy continued with the same treatment. The second trial involved women who were already taking alendronate. They were randomised to one of three treatments: continued alendronate plus parathyroid hormone; continued alendronate plus parathyroid hormone for three cycles of three months alternating with periods of three months without parathyroid hormone; or alendronate alone.

The accompanying editorial (p 624-5) summarises the findings neatly. In terms of bone mineral density, both agents are efficacious as monotherapy. Combination therapy increases central bone mass, but to a lesser extent than parathyroid hormone alone. Bone gained during treatment with parathyroid hormone is lost if no further therapy is implemented. And parathyroid hormone seems to retain its anabolic effect in patients previously treated with a bisphosphonate, although the effect is probably smaller than that seen in previously untreated patients.

New England Journal of Medicine 2005;353:555-65, 566-75

Delayed insertion of tympanostomy tubes does not affect developmental outcomes at age 6

Otitis media with effusion is extremely common in young children, and myringotomy with the insertion of tympanostomy tubes is often undertaken to relieve it, mainly out of concern that the conductive hearing loss associated with otitis media might have lasting adverse effects on cognitive, language, or psychosocial development. It now looks as if this concern may have been exaggerated.

A study in the US enrolled 6350 healthy infants younger than 2 months and evaluated them regularly for middle ear effusion. Those who developed persistent middle ear effusion before the age of 3 years were randomly assigned to have tympanostomy tubes inserted either promptly or, if the effusion persisted, up to nine months later. These children had a full assessment of intelligence, language skills, central auditory processing, behaviours and emotion at the age of 6 years. No significant differences between the groups were seen on any of the 30 measures that were used.

Measures of intellectual and language ability at the age of 6 are strongly predictive of later academic performance so, even though the children continue to be followed up, it seems unlikely that developmental difficulties will become apparent later.

New England Journal of Medicine 2005;353:576-86

Benefits of exercise in older people are influenced by genotype

Older people who keep physically active are less likely to become functionally impaired. Trials of interventions that improve muscle strength and capacity for aerobic exercise have shown benefit in maintaining mobility. But, despite the generally positive effects of exercise, individual responses vary. A study of 3000 people aged 70-79 indicates that this variation may be genetically determined.

Participants were recruited in 1997 and 1998 from two cities in the US and followed up for four years. At the time of enrolment they were all fit and living in the community. Physically active participants (those who reported expending 1000 kcal/week (4.81MJ/week) in exercise, walking, and stair climbing) were less likely to develop mobility limitation (defined as self reported difficulty in walking a quarter of a mile (about 400 m) or up 10 steps in two consecutive interviews six months apart) regardless of angiotensin converting enzyme (ACE) insertion of deletion genotype. After adjusting for potential confounders, however, those with the *II* genotype of the ACE gene were more likely to develop mobility limitation than those with *ID* or *DD* genotypes (adjusted rate ratio, 1.45, 95% CI, 1.08 to 1.94). Among physically inactive participants, the ACE genotype was not associated with mobility limitation. The physiological explanation is uncertain, but it's interesting that the ACE genotype also influences the response to exercise training in young people. The *I* allele is over-represented in elite endurance athletes and in high altitude mountaineers, whereas the *D* allele is found more often among swimmers and sprinters.

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