SHORT CUTS

WHAT'S NEW IN THE OTHER GENERAL JOURNALS

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Be sparing with red cell transfusions in critically ill children

Intensivists should think carefully before giving red cell transfusions to critically ill children, say researchers. A cautious policy that triggers a transfusion only when the haemoglobin concentration drops to 70 g/l (7 g/dl) or below looked safe in a recent trial, and substantially reduced children's exposure to potentially harmful blood products.

The trial included 637 children who were critically ill but stable. All were in paediatric intensive care units. One group had a transfusion threshold of 70 g/l, whereas controls were given red cells when their haemoglobin concentration fell to 95 g/l.

Twelve per cent of both groups (38/320 *v* 39/317) developed new or progressive multiorgan failure. Fourteen children (4%) died in each group. Restricting transfusions made no difference to infection rates, organ dysfunction scores, or duration of illness. But it did reduce children's exposure to red cells by 44% (0.9 *v* 1.7 transfusions per child). Adverse events were closely matched.

The trial was designed specifically to find out if the two strategies were equally safe, and the authors are confident that more judicious use of leucocyte reduced red cells does stable children no harm. The picture may be different for premature babies or children who are hypoxic, haemodynamically unstable, or bleeding.

N Engl J Med 2007;356:1609-19

HRT linked to ovarian cancer

Hormone replacement therapy (HRT) is associated with an increased risk of ovarian cancer in postmenopausal women, according to a large cohort study from the United Kingdom. The risk is small but potentially important and adds up to one extra ovarian cancer for every 2500 women taking HRT for five years. The authors estimate that HRT has been linked to 1300 additional ovarian cancers and 1000 additional deaths in the UK since 1991.

The study tracked more than 900 000 postmenopausal women for an average of seven years. More than 2000 women developed ovarian cancer and 1591 died of it during that time. The relative risk of cancer among current users of any HRT was 1.20 (95% CI 1.09 to 1.32), and the relative risk of death was 1.23 (1.09 to 1.38). The increased risk was confined to women who took HRT for five years or more. Past users were unaffected.

The extra cancers were not due to differences between women who do and do not use HRT, as the authors adjusted their analyses for a dozen potential confounding factors including age, wealth, parity, history of hysterectomy, smoking, body mass index, and time since the menopause.

It's still unclear how or why these hormonal products cause ovarian cancer in older women (if they do). Similar products are protective in premenopausal women.

Lancet 2007
doi: 10.1016/S0140-6736(07)60534-2

New treatment fails to save patients with cardiogenic shock

Cardiogenic shock after myocardial infarction is often lethal. The urgent search for better treatments led scientists to the nitric oxide pathway, which is activated during a heart attack and causes vasodilation and myocardial depression. Preventing the release of nitric oxide by inhibiting the enzyme responsible, nitric oxide synthetase, did not produce the expected survival benefit in a recent placebo controlled trial, however.

The drug tilarginine was so clearly ineffective that researchers stopped recruiting early on the grounds that continuing the study was futile. Patients given the drug were just as likely to die within a month (48%, 97/201) as those given a placebo (42%, 76/180). Tilarginine had no discernible effect on longer term mortality (six months), and it didn't help speed up the resolution of heart failure.

Perhaps the drug failed because it disabled all three isoforms of the enzyme, not just the most harmful one, writes one commentator (pp 1711-3). Or perhaps we simply don't know enough about the nitric oxide pathway to predict reliably what will happen when we inhibit it. But for now it seems clear that non-selective inhibition of nitric oxide synthetase should not be attempted in patients with cardiogenic shock complicating acute myocardial infarction.

JAMA 2007;297:1657-66,1711-3

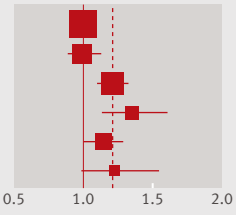
Epoetin is a tempting sideline for dialysis units in the US

Patients with chronic kidney disease often need synthetic erythropoietin to prevent anaemia and keep transfusions to a minimum. But evidence is emerging of systematic overtreatment by some dialysis facilities in the United States. The problem seems to be linked to a perverse reimbursement arrangement with Medicare, whereby facilities can and do profit from treating patients with epoetin, the leading agent.

Four out of five American patients on dialysis are treated in profit making facilities, usually large corporate chains. A careful comparison of these facilities with "not for profit" dialysis units such as those affiliated with hospitals showed a clear difference in treatment patterns. At the end of 2004 (the most recent data available), profit making facilities used more erythropoietin per patient each week, chased and achieved higher haematocrit values, and adjusted patients' doses more aggressively than not for profit units. Patients treated in profit making facilities were more likely to have haematocrit levels higher than the

HRT AND RELATIVE RISK OF OVARIAN CANCER

Last reported HRT use	Years of HRT use	Cases/population (1000s)	Risk ratio (95% CI)
Never users	NA	1142/474.7	1.00
Past users	3.3	391/186.8	0.98 (0.88 to 1.11)
All current users	7.7	740/287.1	1.20 (1.09 to 1.32)
Oestrogen-only	9.2	242/85.9	1.34 (1.13 to 1.60)
Oestrogen + progestogen	6.9	414/169.3	1.14 (1.01 to 1.28)
Other	7.0	84/31.9	1.22 (0.98 to 1.53)



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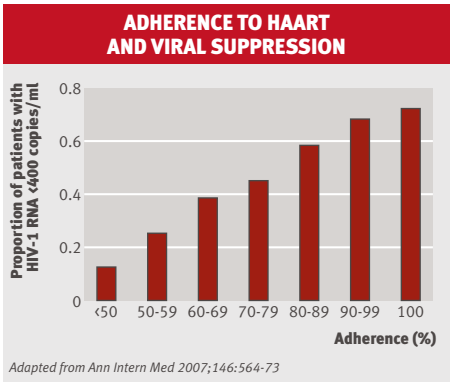
36% target level recommended at the time by national guidelines and by the Food and Drugs Administration (54% *v* 47%).

None of these differences were explained by differences in case mix, and at least one commentator questions whether some units are overtreating patients for profit (pp 1713-6). Last year, the two largest dialysis chains made 21% and 25% of their revenue from epoetin.

JAMA 2007;297:1667-74, ***JAMA*** 2007;297:1713-6

HAART works best when patients adhere to treatment



Highly active antiretroviral therapy (HAART) is an effective treatment for HIV if patients take their drugs as prescribed. Tracking pharmacy claims for reimbursement from insurance companies is one way to measure adherence. It's not ideal, because patients who pick up their drugs at the pharmacy don't necessarily take them, but the method is simple and good enough to give researchers some idea of the link between adherence and viral suppression.

Researchers in South Africa used data from pharmacy claims to study HAART based on non-nucleoside reverse transcriptase inhibitors—the first line option in South Africa and elsewhere. They found a clear and linear relation between sustained viral suppression and better adherence to treatment in 2821 men and women being treated for the first time. Viral suppression started to improve once adherence reached 50%. Above this threshold, each 10% increase in adherence was associated with a 10% increase in the proportion of infected people with a viral load below 400 copies of HIV RNA/ml for a median follow-up of two years. Three quarters of the patients who filled all their prescriptions (100% adherence) reached this target (725/997).

Ann Intern Med 2007;146:564-73

Chondroitin won't relieve the pain of osteoarthritis

A meta-analysis has shown that chondroitin is no better than placebo for reducing the pain of osteoarthritis. A linked editorial (pp 611-2) points out that many patients have a powerful belief in the supplement, and that continuing to take it probably won't do them any harm.

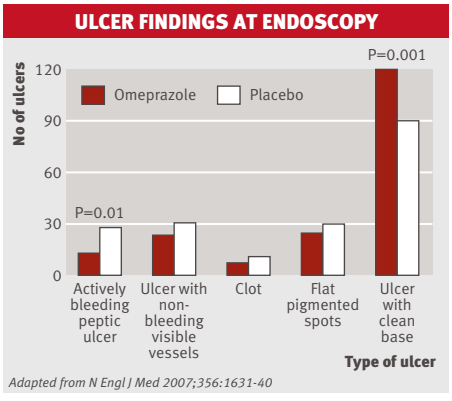
In an unusual step, the researchers chose to focus their analysis on the three biggest and best trials after an initial meta-analysis showed that early trials were small, heterogeneous, poorly done, and potentially biased. As usual, poor quality trials were more likely than better quality trials to report positive results.

The three best trials included 40% of all patients randomised. Most had osteoarthritis of the knee. Together, they suggest that chondroitin takes about half a millimetre off patients' scores on a 10 cm visual analogue scale compared with placebo. The difference was insignificant statistically and barely noticeable clinically. The effect of chondroitin on joint space narrowing was hard to evaluate from the existing data, but the researchers say benefits look unlikely.

This is another example of an intervention that looks useful in early trials but proves not so useful once bigger and better trials are complete, says the editorial.

Ann Intern Med 2007;146:580-90

Researchers recommend omeprazole before endoscopy



Blood doesn't clot well in an acid environment such as the stomach. So researchers in Hong Kong hypothesised that intravenous omeprazole might be a good early treatment for patients waiting for endoscopy after an upper gastrointestinal bleed. They were right. In a randomised trial, patients given a continuous infusion of omeprazole before endoscopy were less likely to need endoscopic treatments to stop the bleeding than patients given placebo (relative risk for the omeprazole group 0.67, 95% CI 0.51 to 0.90). The effect was similar for the subgroup of patients with bleeding peptic ulcers (0.61, 0.44 to 0.84). Treatments included injections of adrenaline around bleeding vessels and thermocoagulation.

Omeprazole didn't reduce patients' transfusion requirements, prevent recurrences, or save lives, and a similar proportion of each group needed emergency surgery to stop the bleeding. But patients given the drug were more likely to make it home from hospital in under three days (60.5% *v* 49.2%, P=0.005).

The researchers say their results confirm the notion that pre-emptive acid suppression can be beneficial for patients who are relatively stable and can afford to wait. But urgent endoscopy must remain the treatment of choice for patients who can't.

N Engl J Med 2007;356:1631-40

Combination therapy helps keep patients with COPD out of hospital

Anticholinergic bronchodilators, long acting β_2 agonists, and inhaled corticosteroids are the mainstays of treatment for people with chronic obstructive pulmonary disease (COPD). Many patients use combinations of all three. Good evidence to support any combination is hard to come by, partly because patients find it hard to stick to their assigned treatment for long enough to show that it works. Still, researchers keep trying, and a team from Canada recently succeeded in reporting some clinically useful results.

In a trial of 449 adults with moderate to severe COPD, the combination of tiotropium, salmeterol, and fluticasone improved lung function and quality of life and reduced admission to hospital compared with tiotropium alone. It did not prevent exacerbations, one of the key aims of treatment. About 60% of patients in each group had an exacerbation requiring treatment with systemic steroids or antibiotics. In a third arm, adding salmeterol to tiopropium worked no better than tiopropium alone.

As expected, the dropout rate was high. More than 40% of patients treated with either tiotropium (74/156) or tiotropium plus salmeterol (64/148) failed to complete their treatment. Many started using inhaled steroids. This crossing over between groups means the negative results from this trial (on exacerbations) are less secure than the positive ones (on admission to hospital), say the authors.

Ann Intern Med 2007;146:545-55