General

No sedation for mechanical ventilation

Standard practice for mechanical ventilation on an intensive care unit (ICU) is to sedate the patient. Studies of daily interruption of sedation have shown that it reduces the duration of mechanical ventilation, possibly reduces the risk of post-traumatic stress disorder, and reduces the risks of ventilator-associated pneumonia, upper gastrointestinal bleeding, bacteraemia, barotraumas, venous thromboembolism, cholestasis, and severe sinusitis. In Odense, Denmark, the practice since 1999 has been to give i.v. morphine but no sedatives or analgesics. Now researchers there have compared no sedation (NS) with daily interrupted sedation (DIS).

A total of 140 patients on mechanical ventilation were randomised to NS or DIS with propofol for 48 hours and then midazolam. Bolus doses of morphine were given in both groups. The analysis included 113 patients. In the first 28 days the mean number of days without ventilation was 13.8 days (NS) vs 9.6 days (DIS), a significant difference. NS was also significantly associated with shorter stay in ICU and in hospital. Agitated delirium was more frequent in the NS group (20% vs 7%). The groups did not differ significantly in the frequency of accidental extubation, ventilator-associated pneumonia, or requests for CT o MRI brain scans.

The NS policy appeared to be advantageous. A multicentre study is called for.

Strøm T et al. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet* 2010; 375: 475–80; Brochard L. Less sedation in intensive care: the pendulum swings back. Ibid: 436–8 (comment).

Procalcitonin-level-guided antibiotic therapy in ICU to reduce antibiotic exposure

Procalcitonin is a calcitonin precursor hormone that serves as a marker of the severity of bacterial infection. Small studies have suggested that use of serial procalcitonin measurements could reduce the length of antibiotic treatment in intensive care units (ICUs), thus inhibiting the development of bacterial antibiotic resistance. Now a multicentre study in France has shown that this can be achieved without compromising clinical outcomes.

A total of 630 adult patients were randomised in eight ICUs to a procalcitonin group and a control group. In the procalcitonin group antibiotic treatment was started and stopped at predefined procalcitonin levels. The controls received antibiotic treatment according to current protocols. Physicians in clinical charge were allowed to make decisions contra to procalcitonin guidelines if they considered it necessary on clinical grounds and did so in 219 episodes. At day 28, mortality was 21.2% (procalcitonin) vs 20.4% (controls). At day 60, the corresponding figures were 30.0% vs 26.1%. Neither difference was significant.

The number of days without antibiotics was 14.3 vs 11.6. The mean duration of antibiotic exposure per 1000 inpatient days was 653 days vs 812 days and the duration of the first course of antibiotics 6.1 days vs 9.9 days. The reduction in duration of the first course of antibiotics was significant for community-acquired pneumonia, ventilator-associated pneumonia, urinary tract infection, and septicaemia.

A procalcitonin-guided policy reduced antibiotic usage without adversely affecting outcomes. Clinicians were allowed to temper procalcitonin guidelines with their clinical instincts.

Bouadma L et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* 2010; 375: 463–74; Kollef MH. Will procalcitonin reduce antibiotic use in intensive care? Ibid: 435–6 (comment).

Stent graft for stenosed dialysis-access grafts

Prosthetic arterio-venous grafts are used to facilitate haemodialysis for patients with chronic renal failure, but they may fail because of venous anastomatic stenosis. Now a US multicentre trial has shown that such stenoses are better dealt with by using a stent graft rather than balloon angioplasty alone.

A total of 190 patients were randomised at 13 centres to balloon angioplasty with or without a stent graft emplacement. Patency at 6 months was achieved in 51% (stent graft) vs 23% (no stent graft), a highly significant difference. Subsequent interventions had been needed by 68% vs 84%. The rate of binary restenosis at 6 months was 28% vs 78%.

Use of a stent graft gave longer and better patency and reduced the need for repeat interventions. An autogenous arteriovenous fistula remains the first choice.

Haskel ZJ et al. Stent graft versus balloon angioplasty for failing dialysis-access grafts. *NEJM* 2010; 362: 494–503; Kerlan RK, LaBerge JM. Fistula first, stent graft second. Ibid: 550–2 (editorial).

Paediatrics

ACSD in West Africa: disappointing results

The Accelerated Child Survival and Development (ACSD) programme was implemented by UNICEF in 11 countries of West and Central Africa between 2001 and 2005 at a cost of US$27 million. By 2005, it was reported that a 20% reduction in mortality in children <5 years old had been achieved in programme areas compared with comparison areas. The programme aimed to speed up reductions in under-5 mortality by focussing on three areas: immunisation plus (including vitamin A supplementation and insecticide-treated bednets), antenatal care, and improved management of pneumonia, malaria, and diarrhoea. The target was a mortality reduction of 25% or more by the end of 2006. An evaluation of the programme in Benin, Ghana, and Mali has been reported.

In Benin and Mali, under-5 mortality decreased less in ACSD areas than in comparison areas (by 13% and 24% in ACSD areas vs 25% and 31% in comparison areas). The absolute decreases in ACSD areas were by 18 deaths per 1000 live births in Benin and 63 per 1000 live births in Mali. The corresponding decreases in non- ACSD areas were 36 and 76 per 1000 live births. In Ghana the decrease was 20% (21 per 1000 live births) but no comparison area data were available. Coverage for preventive interventions increased mre in ACSD areas than in comparison areas in Ghana and Mali but not in Benin. Correct treatment of pneumonia, malaria, and diarrhoea did not change in ACSD areas in Benin and Mali but in Ghana treatment for malaria and diarrhoea deteriorated in ACSD areas.

The disappointing results are attributed to inadequate coverage for treatments of malaria and pneumonia, shortages of insecticide-treated bednets, and failure to address causes of neonatal mortality and undernutrition. Improvements in comparison areas may have masked some improvements in ACSD areas. The *Lancet* calls for more and better evaluation of global health initiatives. A commentator stresses that the focus needs to turn from new technologies to implementation research.

Bryce J et al. The Accelerated Child Survival and Development programme in West Africa: a retrospective evaluation. *Lancet* 2010; 375: 572–82; The Lancet. Evaluation: the top priority for global health. Ibid: 526 (editorial); Peterson S. Assessing the scaleup of child survival interventions. Ibid: 530–1 (comment).

Madhi SA et al. Effect of human rotavirus vaccine on severe diarrhoea in African infants. *NEJM* 2010; 362: 289–98; Richardson V et al. Effect of rotavirus vaccination or death from childhood diarrhoea in Mexico. Ibid: 299–305; Santosham M. Rotavirus vaccine – a powerful tool to combat deaths from diarrhoea. Ibid: 358–60 (editorial).

Effectiveness of rotavirus vaccine in developing countries

It has been suggested that live oral rotavirus vaccines might be less effective in developing countries than in richer countries. Now studies in Africa and Mexico have demonstrated the effectiveness of Rotarix, an attenuated human rotavirus vaccine.

In South Africa and Malawi a total of 4939 infants (3166 in South Africa and 1773 in Malawi) were randomised three ways: two doses of vaccine and one of placebo, three doses of vaccine, or three doses of placebo – the doses given at 6, 10, and 14 weeks.

Severe rotavirus diarrhoea up to the age of 1 year occurred in 1.9% (combined vaccine groups) vs 4.9% (triple placebo group. Overall, vaccine efficacy was 61.2% (58.7% with two doses of vaccine and 63.7% with three). The efficacy was 76.9% in South Africa and 49.4% in Malawi, although more episodes of diarrhoea were prevented in Malawi. Vaccine efficacy against severe gastroenteritis of any cause was 30.2%. The vaccine was well tolerated and mortality was similar (2.5% vs 2.6%) in vaccine and placebo groups. The only case of intussusception occurred in a 6-monthold child who had received three doses of the vaccine.

In Mexico diarrhoea-related mortality fell after the introduction of Rotarix vaccination. The vaccine is given as two doses at 2 and 4 months and vaccination began in 2006. All infants were included from May 2007. In 2003–2006 the average annual under-5-years mortality from diarrhoea was 18.1 deaths per 100 000 children.

By 2008 this figure had fallen to 11.8, a significant 35% reduction. Among infants under 12 months the reduction was 41%. Among children aged 12–23 months, who were mostly unvaccinated, diarrhoea-related mortality fell significantly by 29%, but there was no significant fall among 24–59-month-old children. Reduced diarrhoearelated mortality was seen in the rotavirus seasons of 2008–2009.

The rotavirus vaccine is effective and could do much to limit diarrhoea-related deaths in children around the world.

Surgery

Fundoplication for gastro-oesophageal reflux in children with neurological impairment

Neurologically impaired children are prone to suffer from gastro-oesophageal reflux and to undergo fundoplication but the effectiveness of the operation is uncertain. Now a US study has shown a reduction in reflux-related hospital admissions in the year after operation.

A retrospective, observation cohort study using data from 42 children's hospitals included 3721 neurologically impaired children who had undergone fundoplication out of a total birth cohort of 955 285 children. In the year after operation, hospital admissions for any reflux-related cause were reduced significantly by 31%.

Admissions for aspiration pneumonia were reduced by 29%, and for gastrooesophageal reflux disease by 40%. The need for mechanical ventilation was reduced by 60%. Admissions for any pneumonia remained constant and there was a 52% increase in asthma admissions.

Fundoplication reduced reflux-related hospital admissions in the year after the procedure.

Srivastava R et al. Reflux related hospital admissions after fundoplication in children with neurological impairment: retrospective cohort study. *BMJ* 2010; 340: 85 (2009; 339: b4411).

Biliary drainage before surgery for cancer of the head of the pancreas

Preoperative biliary drainage for patients with obstructive jaundice due to cancer of the head of the pancreas was introduced to reduce complication rates. There is evidence, however, that the complications associated with the drainage procedure plus those occurring after surgery might add up to a bigger burden than if preoperative drainage were not done. Now a multicentre trial in The Netherlands has shown an increased complication rate with preoperative drainage,

The trial included 202 patients and 196 were included in the analysis. All had cancer of the head of the pancreas and obstructive jaundice with a bilirubin level of 40– 250 µmol/L (2.3–14.6 mg/dl). Randomisation was to surgery alone or preceded by 4–6 weeks of biliary drainage, usually via a stent inserted using endoscopic retrograde cholangiopancreatography (ERCP). Serious complications occurred in 39% (surgery alone) versus 74% (drainage). The drainage procedure was successful after one or more attempts in 94% of patients and led to complications, mostly cholangitis, pancreatitis, or need to change the stent, in 46%. Complications of surgery occurred in 37% of the surgery alone group and 47% of the preoperative drainage group. Delayed gastric emptying, wound infection, pneumonia, and cholangitis were more frequent in the drainage group. Overall mortality and length of hospital stay were similar in the two groups.

Routine preoperative biliary drainage led to more complications. The use of selfexpanding metallic stents (SEMS) rather than the plastic stents used in this trial might prevent stent occlusion.

Van der Gaag NA et al. Preoperative biliary drainage for cancer of the head of the pancreas. *NEJM* 2010; 362: 129–37; Baron TH, Kozarek RA. Preoperative biliary stents in pancreatic cancer – proceed with caution. Ibid: 170–2 (editorial).

Nasal decontamination to reduce surgical wound infections

People who carry *Staphylococcus aureus* in their noses are more likely to have surgical wound infection. Trials of nasal decontamination have given disappointing results but the treatment may have been given too late and skin decontamination was not carried out. Now researchers in The Netherlands have had success with rapid testing for nasal carriage, mupirocin nasal ointment, and chlorhexidine soap.

In a multicentre trial a total of 6771 adult patients admitted to medical or surgical wards were screened for nasal carriage of *S aureus* by real-time PCR. Nasal carriage was demonstrated in 1251 patients, of whom 917 entered the trial with randomisation to mupirocin nasal ointment and chlorhexidine soap or placebo ointment and soap. All the strains of *S aureus* detected were susceptible to mupirocin and methicillin. Of the 917 patients, 808 underwent surgery. *S aureus* infection occurred in 3.4% (treatment) and 7.7% (placebo), a significant 58% reduction in the treatment group. For deep surgical-site infections there was a 79% reduction. The time to onset

of infection was longer in the treatment group. All-cause, in-hospital mortality was similar in the two groups.

Rapid screening for nasal *S aureus* and treatment with nasal mupirocin and chlorhexidine soap reduced the incidence of surgical-site infections. An editorialist suggests that this process could be reserved for patients undergoing cardiac surgery, those receiving an implant, and immunosuppressed patients undergoing surgery.

Bode LGM et al. Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. *NEJM* 2010; 362: 9–17; Wenzel RP. Minimizing surgical-site infections. Ibid: 75–7 (editorial).

Tropical

Single-dose liposomal amphotericin B for visceral leishmaniasis

More than half of the world's people with visceral leishmaniasis live in India and almost half of the Indian patients live in the state of Bihar. Treatment with liposomal amphoteracin B in short courses is effective but single infusions of 5 or 7.5 mg/kg gave cure rates of <95%. Recently, reduced cost has made larger single doses possible and researchers in Bihar have obtained satisfactory results with a single dose of 10§mg/kg.

A total of 412 patients were randomised (3:1) to a single i.v. infusion of liposomal amphoteracin B, 10§mg/kg with discharge the following day or amphoteracin B deoxycholate (15 alternate-day infusions, each of 1 mg/kg, in hospital over a period of 29 days). Apparent cure at 30 days was recorded for all patients in the liposomal amphoteracin group and 98% in the control group. At 6 months the cure rates were 95.7% and 96.3%. Infusion-related fever or rigors occurred in 40% vs 64%.

Increased anaemia or thrombocytopenia occurred in 2% of the liposomal group and increased anaemia in 19% of the control group. Nephrotoxicity or hepatotoxicity were uncommon (up to 1% in each group). Hypokalaemia occurred in two patients in the control group. The cost of treatment was estimated at US$162 for liposomal amphoteracin B and US$436 for amphoteracin B deoxycholate.

A single infusion of liposomal amphoteracin B was not inferior to, and less expensive than, conventional therapy with amphoteracin B deoxycholate. Liposomal treatment entailed 24 hours in hospital whereas the conventional therapy meant 29 days in hospital.

Sundar S et al. Single-dose liposomal amphoteracin B for visceral leishmaniasis in India. *NEJM* 2010; 362: 504–12.

AIDS

Antiretroviral therapy in Africa: routine vs clinically-driven laboratory monitoring

In Africa, many people have been given access to antiretroviral therapy (ART) for the first time and resources often do not run to routine laboratory monitoring. There is debate about whether available resources should be extended to provision of monitoring or should be concentrated on extending drug treatment to as many people as possible. The DART (Development of AntiRetroviral Therapy in Africa) trial was designed to assess the importance and desirability of routine monitoring of therapy.

At three centres in Uganda and one in Zimbabwe, a total of 3321 symptomatic, ARTnaïve, HIV-infected adults with CD4 counts <200 cells per µL and about to start ART, were randomised to routine laboratory and clinical monitoring (LCM) or clinically driven monitoring (CDM). Both groups had haematology, biochemistry, and CD4-cell counts every 12 weeks but results were sent to clinicians routinely only in the LCM group. Clinicians caring for CDM-group patients were provided with results (no CD4 counts) only on request because of clinical indications or grade 4 toxicity. A switch to second-line ART was made with new or recurrent WHO stage 4 events or (in theLCM group) with a CD4 count <100 cells per µL. The rate of 5-year survival was 87% (CDM) vs 90% (LCM). Average follow-up was 4.9 years., The rates of death or a new WHO stage 4 event were 28% (CDM) vs 21% (LCM), equivalent to 6.94 vs 5.24 per 100 person-years, a highly significant 31% relative increase in the CDM group. A new serious adverse event, most commonly anaemia, occurred in 17% vs 16%. Differences in disease progression occurred from the third year of treatment. Rates of switch to second-line treatment were higher in the LCM group from the second year.

It is concluded that ART can be given safely without routine laboratory monitoring for toxic effects but CD4-cell count monitoring from the second year of ART would guide the switch to second-line treatment.

DART Trial Team. Routine versus clinically driven laboratory monitoring of HIV anti-retroviral therapy in Africa (DART): a randomised non-inferiority trial. *Lancet* 2010; 375: 123–31; Phillips A, van Oosterhout J. DART points the way for HIV treatment programmes. Ibid: 96–8 (comment).

Home-based vs clinic-based care

Although more than 2 million people are now taking anti-retroviral therapy in Africa, another 5 million do not yet have access to it. The two main barriers are a lack of health workers and difficulty of access to clinics. Increased provision via nurse-led rural clinics may partially alleviate the problem but further improvement may depend on the use of lay workers. Now a study in Uganda has shown that home care may be as effective as clinic care.

A total of 44 geographical areas (1453 patients) were randomised to home or clinic care (859 patients and 594 patients respectively). Antiretroviral therapy was started at the central clinic. The home-care group were then visited once a month by trained lay field officers who provided drugs and monitored and supervised treatment. The clinic care group attended the clinic regularly for supervision and drug supply. In the first year mortality was the same (11%) in the two groups. The withdrawal rate was 3% (home) vs 6% (clinic) and loss to follow-up 1% vs 2%. Rates of virological failure were similar in the two groups: 16% (8.2 per 100 person-years) vs 17% (8.7 per 100 person-years). Rates of hospital admission were 11% vs 13%. The cost to the health service was US$793 (home care) vs US$838 (clinic care) per year. The cost to the patients was US$29 vs US$60 in the first year and US$18 vs US$54 per year thereafter, the differences being accounted for mostly by the cost of getting to the clinic.

Home-based care was as effective as clinic-based care and could improve access to care.

Jaffar S et al. Rates of virological failure in patients treated in a home-based versus a facility-based HIV-care model in Jinja, southeast Uganda: a cluster-randomised equivalence trial. *Lancet* 2009; 374: 2080–9; Korenromp EL, Viisainen KM. ART in rural Uganda- efficient scale-up with home-based care? Ibid: 2034–5 (comment).

Switching from lopinavir-ritonavir to raltegravir

Antiretroviral treatment based on lopinavir-ritonavir is effective but may cause lipid abnormalities and other undesir-

able effects and a switch to another regimen might be considered. Raltegravir is a new drug that acts as an HIV-1 integrase strand transfer inhibitor. A switch from lopinavir-ritonavir to raltegravir-based treatment has been assessed in two international trials reported together.

In two multicentre trials carried out at 81 centres on five continents, a total of 702 adult patients taking a lopinavir-ritonavir-based regimen were randomised to continue the same treatment or to switch to raltegravir. All patients had had undetectable viral RNA levels for at least 3 months on lopinavir-ritonavir and continued to take at least two nucleoside or nucleotide reverse transcriptase inhibitors. In the first 12 weeks lipid concentrations fell in the switch group and rose in the continuation group. The changes were: (switch vs continue) total cholesterol –12.6% vs +1.0%, non-HDL cholesterol –15.0% vs +2.6%, triglycerides –42.2% vs +6.2%. Viral RNA concentration at week 24 was <50 copies per ml in 90.6% of the continuation group and 84.4% of the switch group. Adverse event frequencies were similar in the two groups. The trials were stopped at 24 weeks because of lower virological efficacy in the raltegravir group.

Switching to raltegravir improved lipid profiles but was associated with deterioration in viral efficacy.

Eron JJ et al. Switch to a raltegravir-based regimen versus continuation of a lopinavirritonavir- based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. *Lancet* 2010; 374: 396–407; Kilby JM. Switching HIV therapies: competing host and viral factors. Ibid: 352–4 (comment).

Obs & Gyn

Internal tocodynamometry: no advance on external?

Internal tocodynamometry to monitor uterine contractions has been widely recommended for use after induction or augmentation of labour. Several small trials, however, have failed to show any clinical benefits from internal, as opposed to external, tocodynamometry. Now a large multicentre trial in The Netherlands has given similar results.

A total of 1456 women needing induced or augmented labour were randomised at six centres to internal or external tocodynamometry. The rate of operative delivery was 31.3% (internal) vs 29.6% (external), a nonsignificant difference. Adverse neonatal outcomes occurred in 14.3% vs 15.0% and the rates of other secondary outcomes (low Apgar score at 5 minutes, neonatal hospital stay >48 hours) were similar in the two groups. There were no serious adverse effects of internal monitoring via an intrauterine catheter.

Internal tocodynamometry did not improve outcomes compared with external monitoring.

Bakker JJH et al. Outcomes after internal versus external tocodynamometry for monitoring labor. *NEJM* 2010; 362: 306–13.

Misoprostol for post-partum haemorrhage in women not given oxytocin in labour

The mortality from post-partum haemorrhage (PPH) in developing countries is 100 times that in developed countries. The standard drug, oxytocin, is often not available in developing countries because it needs refrigeration, skilled attendants, and i.v. administration. Sublingual misoprostol might be a valuable alternative in situations where these are lacking. Now two multicentre trials in developing countries have shown the feasibility of using sublingual misoprostol.

In hospitals in Ecuador, Egypt, and Vietnam a total of 9348 women not given prophylactic oxytocin in labour were observed and 978 developed PPH. The women with PPH were randomised to sublingual misoprostol (800 µg) or i.v. oxytocin (40 IU). Active bleeding stopped within 20 minutes in 90% (misoprostol) vs 96% (oxytocin). Loss of an additional 300 ml or more of blood after treatment was documented in 30% vs 17%. Shivering occurred in 47% vs 17% and fever in 44% vs 6%. There were no deaths or hysterectomies.

Misoprostol might be used where oxytocin is not available for PPH. (But oxytocin should be made available).

Winikoff B et al. Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomised, non-inferiority trial. *Lancet* 2010; 375: 210–6; Buekens P, Althabe F. Post-partum haemorrhage: beyond the confrontation between misoprostol and oxytocin. Ibid: 176–8 (comment).

Misoprostol for PPH after prophylactic oxytocin

Misoprostol may be used to treat PPH when oxytocin is not available (see above). A trial in Burkina Faso, Egypt, Turkey, and Vietnam included 809 women with PPH out of a total of 31 055 women given prophylactic oxytocin after delivery of the baby.

The women with PPH were randomised to sublingual misoprostol (800 µg) or i.v. oxytocin (40 IU). Active bleeding stopped within 20 minutes in 89% (misoprostol) vs 90% (oxytocin). Additional blood loss of at least 300 ml occurred in 34% vs 31%.

Shivering occurred in 37% vs 15% and fever in 22% vs 15%. There were two deaths (one in each group) and six hysterectomies (four in the misoprostol group and two in the oxytocin group).

Misoprostol is clinically equivalent to oxytocin for the treatment of PPH in women given prophylactic oxytocin during the third stage of labour.

Blum J et al. Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women receiving prophylactic oxytocin: a double-blind, randomised, non-inferiority trial. *Lancet* 2010; 375: 217–23; Buekens P, Althabe F. Post-partum haemorrhage: beyond the confrontation between misoprostol and oxytocin. Ibid: 176–8 (comment).

Infection

DNA-based microarray platforms for rapid identification of bacterial species

New DNA-based microarray platforms allow rapid identification of bacterial species in cases of sepsis. Now the method has been assessed at two teaching hospital laboratories in Helsinki and London.

A total of 2107 positive blood culture samples were examined by conventional culture methods and by a DNA-based microarray platform assay (Prove-it sepsis assay) that identifies more than 50 species of gram-positive and gram-negative bacteria. A pathogen covered by the assay was detected in 1807 (86%) of the positive blood culture samples and 50% of all blood cultures. Among species covered by the assay it identified 97.1% of gram-positive and 96.7% of gram-negative bacteria identified by standard blood culture methods including all 16 cultures of meticillin-resistant *Staphylococcus aureus*. In 341 samples, bacterial species not covered by the assay were identified by blood culture, mainly *Streptococcus viridans* and *Candida spp*.

Overall the sepsis assay had a sensitivity of 94.7% and a specificity of 98.8% when compared with conventional blood culture. Results of the sepsis assay were available during the same working day and, on average, 18 hours 19

minutes earlier than with the reference method. There was an increase in false negatives in polybacterial samples.

The sepsis assay was highly sensitive and specific and faster than conventional methods. It is potentially adaptable for use in developing countries. Issues of cost will need to be addressed.

Tissari P et al. Accurate and rapid identification of bacterial species from positive blood cultures with a DNA-based microarray platform: an observational study. *Lancet* 2010; 375: 224–30; Lin S, Yang S. Molecular methods for pathogen detection in blood. Ibid: 178–9 (comment).

Antibody therapy for *Clostridium difficile* infection

Infection with *Clostridium difficile* has become more prevalent and more severe in Europe and North America in recent years. Now researchers in the USA and Canada have developed monoclonal antibodies against *C difficile* toxins A and B and shown them to be effective in preventing recurrent *C difficile* infection.

A total of 200 adults who had had C. difficile diarrhoea in the last 14 days, continuing at the time of enrolment and treated with metronidazole or vancomycin, were randomised at 30 centres to receive an infusion of both antibodies, each at a dose of 10 mg/kg, or placebo. Recurrence of *C difficile* infection within 84 days occurred in 7% (antibodies) vs 25% (placebo), a highly significant difference. Among patients infected with the highly virulent, epidemic strain (BI/NAP1/027) the reinfection rates were 8% vs 32% and among patients with more than one previous episode the rates were 7% vs 38%. Serious adverse events were more common in the placebo group.

Treatment with antitoxin monoclonal antibodies reduced the risk of recurrence.

Lowy I et al. Treatment with monoclonal antibodies against Clostridium difficile toxins. *NEJM* 2010; 362: 197–205; Kyne L. Clostridium difficile – beyond antibiotics. Ibid: 264–5 (editorial).

Diabetes

Hypoglycaemia and mortality in type 2 diabetes

Data from the ACCORD study of intensive versus standard glucose control in type 2 diabetes have shown the importance of avoiding severe hypoglycaemia.

Two retrospective studies included over 10 000 patients at high cardiovascular risk with an average follow-up of 3.5 years. Among patients in the intensive control arm, annual mortality was 2.8% if there had been at least one episode of hypoglycaemia requiring assistance and 1.2% among other patients. The corresponding proportions in the standard control arm were 3.7% and 1.0%. The annual incidence of hypoglycaemia was 3.14% (intensive control) vs 1.03% (standard control). Increased risk of hypoglycaemia was related to sex (women >men) race (African–Americans >whites), less than high school education, increased age, and use of insulin at trial entry. The risk was lower among patients with a more rapid fall in HbA_{1c} concentration in the first 4 months of the trial.

The occurrence of severe hypoglycaemia is associated with increased mortality among patients with type 2 diabetes and other cardiovascular risk factors.

Bonds DE et al. The association between symptomatic, severe hypoglycaemia, and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ* 2010; 340: 137 (2009; 339: b4909); Miller ME et al. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD STUDY. Ibid: 138 (b5444).

HbA_{1c} and survival in type 2 diabetes

Among people with type 2 diabetes both high and low blood glucose levels may be associated with increased morbidity and mortality. A retrospective cohort study based on the UK General Practice Research Database has provided more data.

Two cohorts of patients aged 50 years or older with type 2 diabetes were generated from the database. There were 27 965 patients who had changed from oral monotherapy to oral therapy with more than one drug and 20005 who had changed to added insulin. The HbA_{1c} level associated with the lowest mortality was around 7.5%.

The lowest HbA_{1c} level (lowest decile) of around 6.4% was associated with a 52% increase in mortality compared with the most favourable decile and the highest decile (around 10.5%) for HbA_{1c} was associated with a 79% increase in mortality above that of the most favourable decile. There was a J-shaped curve for mortality against HbA_{1c} among people on combined oral therapy and a U-shaped curve among people on added insulin. All-cause mortality was 50% higher among people on insulin-based treatment than among people on combined oral agents.

Both low and high HbA_{1c} levels are associated with increased all-cause mortality in people with type 2 diabetes. Diabetes guidelines may need to be revised to include a minimum value for acceptable HbA_{1c}.

Currie CJ et al. Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study. *Lancet* 2010; 375: 481–9; Balkau B, Simon D. Survival in people with type 2 diabetes as a function of HbA1c (comment).

Cardiology

Calcium channel blockers, diuretics, and myocardial infarction

Many patients with hypertension are treated with two drugs including a diuretic. Now a study in Washington State, USA has linked therapy with a diuretic and a calcium channel blocker with increased risk of myocardial infarction.

The case-control study was based on a large health maintenance organisation. Cases were people aged 30–79 who were receiving antihypertensive drug treatment and had had a myocardial infarction or a stroke between 1989 and 2005. Matched controls were treated for hypertension but had not had myocardial infarction or stroke. There were 952 controls, 211 cases with myocardial infarction and 142 cases with stroke.

Among the 1305 participants, 629 were treated with a diuretic and a β–blocker, 273 with a diuretic and a calcium channel blocker, and 403 with a diuretic and an ACE inhibitor or an angiotensin receptor blocker (ARB). Compared with diuretic plus β–blocker, treatment with diuretic plus calcium channel blocker was associated with a 98% increase in risk of myocardial infarction but no increase in risk of stroke. For diuretic plus ACE inhibitor or ARB there was a non-significant reduction in risk of myocardial infarction or stroke compared with diuretic plus β–blocker.

Treatment with a diuretic plus a calcium channel blocker may be associated with increased risk of myocardial infarction compared with treatment with a diuretic plus either a β–blocker or an ACE inhibitor or ARB.

Boger-Megiddo I et al. Myocardial infarction and stroke associated with diuretic based two drug antihypertensive regimens: population based case-control study. *BMJ* 2010; 340: 303 (c103).

Ticagrelor vs clopidogrel for coronary intervention

A large international trial has shown that ticagrelor, a reversible, direct-acting oral P2Y12-receptor antagonist, has advantages over clopidogrel for

patients with acute coronary syndromes scheduled for an invasive strategy.

The study, at 862 centres in 43 countries, included 13 408 patients with acute coronary syndromes, with or without ST-segment elevation, for whom an invasive strategy was planned. Randomisation was to oral ticagrelor (180 mg followed by 90 mg twice daily) or oral clopidogrel (300 mg followed by 75 mg daily) for 6–12 months. All patients also received aspirin. The primary composite endpoint (cardiovascular death, myocardial infarction, or stroke) occurred in significantly fewer patients in the ticagrelor group (9.0% vs 10.7% at 360 days). There were no significant differences in rates of bleeding: total major bleeding 11.5% (ticagrelor) vs 11.6% (clopidogrel), severe bleeding 2.9% vs 3.2%.

These researchers conclude that ticagrelor seems to be the better option.

Cannon CP et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet* 210; 375: 283–93; Stone GW. Ticagrelor in ACS: redefining a new standard of care? Ibid: 263–5 (comment).

Intravenous iron for heart failure and iron deficiency

People with heart failure may be at increased risk of developing iron deficiency, which in turn, may aggravate the heart failure. There is evidence from small studies that intravenous iron may be effective in these patients. Now a large, international trial has confirmed the benefits.

The trial, at 75 sites in 11 European countries, included 459 patients with chronic heart failure (NYHA class II or III) low left ventricular ejection fraction, iron deficiency and haemoglobin 95–135 g/L. They were randomised (2:1) to i.v. ferric carboxymaltose (200 mg iron) weekly until iron repletion then every 4 weeks, or saline placebo. At week 24, significantly more patients in the iron group (50% vs 28%) reported much or moderate improvement on the Patient Global Assessment scale. A heart failure class of I or II was recorded for 47% vs 30%. Patients in the iron group were 2.4 times more likely to have improved by one class. The improvement occurred in patients with or without anaemia. There were also improvements in distance walked in 6 minutes and in quality of life. Treatment did not affect mortality or rate of adverse events.

Treatment with i.v. iron is effective and safe for people with heart failure and iron deficiency. It has not been proved that i.v. iron is better than oral iron.

Anker SD et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *NEJM* 2009; 361: 2436–48; Dec GW. Anemia and iron deficiency – new therapeutic targets in heart failure? Ibid: 2475–7.

Dermatology

Ustekinumab vs etanercept for psoriasis

Proinflammatory cytokines are important in the pathogenesis of psoriasis. Now two anticytokine agents have been compared for the treatment of psoriasis in an international trial; a TNF-α inhibitor (etanercept) and a blocker of interleukins-12 and 23 (ustekinumab).

A total of 903 patients with moderate-to-severe psoriasis were randomised at 67 sites worldwide to ustekinumab 45 mg or 90 mg at weeks 0 and 4 or high-dose etanercept (50 mg twice weekly for 12 weeks). An improvement of at least 75% in the psoriasis area-and-severity index (PASI) at week 12 was achieved by 67.5% (ustekinumab 45 mg), 73.8% (ustekinumab 90 mg) and 56.8% (etanercept), a significant difference between etanercept and either dose of ustekinumab. On the physician's global assessment there was clearing of psoriasis or minimal remaining disease in 65.1% (45 mg). 70.6% (90 mg), and 49% (etanercept). After week 12, patients in the etanercept group who had not responded were switched to ustekinumab and 48.9% had at least a 75% PASI improvement within 12 weeks of the switch. Adverse events in the first 12 weeks of the trial occurred in 66.0% (45 mg), 69.2% (90 mg), and 70% (etanercept) and were serious in 1.9%, 1.2, and 1.2%, respectively.

Better results were obtained with ustekinumab at either dosage than with high-dose etanercept.

Griffiths CEM et al. Comparison of ustekinumab and etanercept for moderate-tosevere psoriasis. *NEJM* 2010; 362: 118–28.

Oncology

Physiotherapy to prevent lymphoedema after breast cancer surgery

A study in Madrid, Spain has confirmed that early postoperative physiotherapy after breast cancer surgery with axillary lymph node dissection prevents lymphoedema.

A total of 120 women were randomised to physiotherapy (manual lymph drainage, massage of the scar, progressive active and active-assisted shoulder exercises, and education) or no physiotherapy after operation. Lymphoedema developed in 7% (physiotherapy) vs 25% (controls). The average increase in volume ratio (affected arm: unaffected) was 1.6% vs 5.1%. The time to onset of lymphoedema was four times longer in the physiotherapy group.

Early physiotherapy reduces the risk of postoperative lymphoedema in the first year.

Lacomba MT et al. Effectiveness of early physiotherapy to prevent lymphoedema after surgery for breast cancer: randomised, single blinded, clinical trial. *BMJ* 2010; 340: 140 (b5396); Cheville A. Prevention of lymphoedema after axillary surgery for breast cancer. Ibid: 110–1 (b5235) (editorial).

Trastuzumab with chemotherapy for HER2-positive locally advanced breast cancer

Trastuzumab is a recombinant humanised monoclonal antibody against human epidermal growth factor receptor-2 (HER2) used as monotherapy or with chemotherapy for HER2-positive, metastatic or early operable breast cancer. Now an international trial has shown that the addition of pre-and post-operative (neoadjuvant and adjuvant) trastuzumab to preoperative chemotherapy improves results in women with HER2-positive locally advanced or inflammatory breast cancer.

A total of 235 women with these types of breast cancer were given neoadjuvant treatment with doxorubicin, paclitaxel, cyclophosphamide, methotrexate, and fluorouracil and randomised to trastuzumab (neoadjuvant and adjuvant) or no trastuzumab, for 1 year. The 3-year event-free survival rate was 71% with trastuzumab and 56% without, a significant 41% improvement with trastuzumab. Trastuzumab was well tolerated and, although it was given with doxorubicin, only two patients developed symptomatic heart failure and both responded to medical treatment. The results of chemotherapy were similar in HER2-positive and HER2 – negative groups.

These researchers conclude that neoadjuvant and adjuvant trastuzumab should be considered for women with HER2-positive locally advance or inflammatory breast cancer.

Gianni L et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet 1020; 375: 377–84: Seal MD, Chia SK. Challenging the dogma on trastuzumab: a matter of heart. Ibid: 349–50.