

## General

### Dopamine vs norepinephrine for shock

Both dopamine and norepinephrine (noradrenaline) are used to treat shock but there is no agreement about which is better. Now a trial in Belgium, Austria, and Spain has provided evidence that norepinephrine may be the better drug.

A total of 1679 patients with shock were randomised at eight centres to dopamine (up to 20 µg/kg/min) or norepinephrine (up to 0.19 µg/kg/min). If blood pressure was not maintained at these doses open-label norepinephrine, epinephrine, or vasopressin could be added. Mortality at 28 days was similar in the two groups (dopamine 52.5%, norepinephrine 48.5%). Arrhythmias, however, were significantly more frequent with dopamine (24.1% vs 12.4%). Dopamine was associated with a significantly higher 28-day mortality than was norepinephrine among the 280 patients with cardiogenic shock. Among the 1044 patients with septic shock and the 263 with hypovolaemic shock 28-day mortality with dopamine was not significantly greater than with norepinephrine. Overall, mortality at 1 year was 65.9% (dopamine) vs 63.0% (norepinephrine), a nonsignificant difference.

Although the two drugs were associated with similar rates of mortality, dopamine may be more dangerous.  
De Backer D et al. Comparison of dopamine and norepinephrine in the treatment of shock. *NEJM* 2010; 362: 779–89; Levy JH. Treating shock – old drugs, new ideas. *Ibid*: 841–3 (editorial).

### Prophylactic antibiotics for burns patients

Current guidelines do not recommend prophylactic systemic antibiotics for patients with burns, although some recommend such prophylaxis to cover operative procedures and some recommend topical antibiotics. A systematic review and meta-analysis has provided evidence in favour of routine systemic antibiotic prophylaxis.

The analysis included 17 studies, 12 of which assessed systemic antibiotic prophylaxis. Such prophylaxis for 4–14 days after admission reduced all-cause mortality significantly, by 46%, and pneumonia by 45%. Perioperative systemic antibiotics decreased wound infections by 28% but did not affect mortality. Topical antibiotics provided no benefit. Systemic antibiotic prophylaxis

reduced the risk of infection with Gram-positive bacteria but not Gram-negative. Infections with *Staphylococcus aureus* were reduced by 42%.

Systemic antibiotic prophylaxis is beneficial for burns patients.

Avner T et al. Prophylactic antibiotics for burns patients: systematic review and meta-analysis. *BMJ* 2010; 340: 517 (c 241).

## Paediatrics

### Treatment of asthma for children not controlled on low-dose inhaled steroid

There is uncertainty about the best treatment for children whose asthma is not well controlled on low-dose inhaled steroid. A US multicentre trial has provided evidence in favour of adding salmeterol but there are doubts about the long-term safety of salmeterol.

A total of 182 children aged 6–17 years whose asthma was not controlled on inhaled fluticasone 100 µg twice daily were randomised to one of three options: increased fluticasone (250 µg twice daily, F+); addition of salmeterol (fluticasone 100 µg twice daily plus salmeterol 50 µg twice daily, F+S); or addition of montelukast (fluticasone 100 µg twice daily plus montelukast 5 or 10 mg daily, F+M). Each child received each treatment in a 3 × 16-week, triple-cross-over design. The composite outcome included exacerbations, asthma-control days, and FEV1. The responses to F+S were 60% better than to F+M and 70% better than to F+. Good responses to salmeterol were more likely in children whose asthma was better controlled at baseline. Some children responded better to F+M of F+.

Although this trial provides evidence in favour of adding salmeterol, editorialists prefer either increasing the dose of fluticasone or adding montelukast because of concerns about the long-term safety of salmeterol. Whichever treatment is chosen close follow-up is necessary.

Lemanske RF et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *NEJM* 2010; 362: 975–85; Von Mutius E, Dragen JM. Choosing asthma step-up care. *Ibid*: 1042–3 (editorial).

### Training in newborn care in developing countries: no effect on perinatal mortality

Worldwide, there are about 3.7 million neonatal deaths and 3.3 million still-

births each year. The major causes of perinatal mortality are birth asphyxia, low birth weight, and prematurity. There is evidence that training for birth attendants in developing countries could reduce perinatal mortality. Now a study in six countries (Argentina, Democratic Republic of Congo, Guatemala, India, Pakistan, and Zambia) has shown no improvement in early neonatal mortality (first 7 days) after such training.

Local instructors in the six countries trained rural birth attendants in the WHO Essential Newborn Care course (routine neonatal skin care, resuscitation, thermo-regulation, breast feeding, 'kangaroo' (skin-to-skin) care, care of the small baby, and common illnesses). They also used the American Academy of Pediatrics (AAP) Neonatal Resuscitation Program providing further training in neonatal resuscitation. A total of 57 643 infants were involved in the assessment of the WHO course and 62 366 in the AAP course. After the WHO training there was no significant reduction in early neonatal mortality or perinatal mortality. The stillbirth rate fell significantly by 30%. Further training in neonatal resuscitation using the AAP programme provided no significant benefit in terms of any of these indicators.

Training of birth attendants did not reduce early neonatal or perinatal mortality. The reduction in stillbirths may have resulted from a reclassification of some stillbirths as live births.

Carlo WA et al. Newborn-care training and perinatal mortality in developing countries. *NEJM* 2010; 362: 614–23.

### Out of hospital cardiac arrest in children: compression only versus conventional resuscitation

Resuscitation by bystanders using compression only has been recommended for out-of-hospital cardiac arrest in adults but not in children. A study in Japan has shown that compression-only resuscitation is as effective as conventional resuscitation with rescue breathing for children with cardiac arrest of cardiac cause but not for those with cardiac arrest of noncardiac cause (many cardiac arrests outside hospital in children have a respiratory cause).

A total of 5170 children aged up to 17 years were included in the study in the years 2005, 2006, and 2007; 3675 with out-of-hospital cardiac arrest of noncardiac cause and 1495 with out-of-hospital cardiac arrest of cardiac cause. Children given cardiopulmonary resuscitation

(CPR) by a bystander were more likely to have a favourable neurological outcome than children not given CPR (4.5% vs 1.9%). For children with arrest of non-cardiac cause treated by a bystander the rate of favourable neurological outcome was 7.2% with conventional CPR but only 1.6% with compression only CPR. For children with arrest of cardiac cause the outcome was similar after bystander CPR using conventional or compression-only techniques (9.9% vs 8.9% favourable). Outcomes in infants were poor (1.7% favourable with either technique).

For children with cardiac arrest of noncardiac cause treated by a bystander conventional CPR with rescue breathing is more effective than compression only. When the cardiac arrest is of cardiac cause either technique could be used.

Kitamura T et al. Conventional and chest compression only cardiopulmonary resuscitation by bystanders for children who have out-of-hospital cardiac arrests: a prospective, nationwide, population-based cohort study. *Lancet* 2010; 375: 1347–54; López-Herce J, Álvarez AC. Bystander CPR for paediatric out-of-hospital cardiac arrest. *Ibid*: 1321–2 (comment).

## Tropical

### Treatment for Buruli ulcer

Buruli ulcer is characterised by subcutaneous necrosis: its cause is infection with *Mycobacterium ulcerans*. The name comes from Buruli County in Uganda where the disease was common 50 years ago. Now there are many cases in West Africa each year, mainly in children. The ulcers may become very large (>15 cm) and they may cause scarring and joint contractures and may affect sites such as the eyes, breasts, and genitalia. Diagnosis may be aided by PCR (Polymerase Chain Reaction). Treatment has been with surgical debridement, but in 2004 WHO recommended adding antimycobacterial drugs (streptomycin and rifampicin). Now a trial in Ghana has confirmed the effectiveness of antimycobacterial treatment.

The trial included 151 children and young adults with early (<6 months), limited (<10cm), PCR-confirmed, *M. ulcerans* ulceration. Randomisation was to 8 weeks of i.m. streptomycin plus oral rifampicin (8 weeks) or 4 weeks of this treatment followed by 4 weeks of oral rifampicin and clarithromycin (4+4 weeks). Treatment was directly observed (DOT) and surgical debridement was performed as deemed necessary. At 1 year the lesions had healed in 96% (8

weeks) vs 91% (4+4 weeks), a nonsignificant difference. No lesions healed and then recurred within the year. Three patients, one in the 8-week group and two in the 4+4-week group, had ototoxicity. Three patients in the 4+4-week group developed abscesses. Time to healing averaged 18 weeks for smaller lesions and 30 weeks for larger.

The treatment was effective in both groups. The number of injections of streptomycin can be reduced by changing to clarithromycin after 4 weeks.

Nienhuis WA et al. Antimicrobial treatment for early, limited *Mycobacterium ulcerans* infection: a randomised controlled trial. *Lancet* 2010; 375: 664–72; Johnson PDR. Should antibiotics be given for Buruli ulcer? *Ibid*: 618–9 (comment).

### Neonatal vitamin A and mortality in low birthweight infants in Guinea-Bissau

There is uncertainty about the effects of neonatal vitamin A supplementation on infant mortality in developing countries. A trial in Guinea-Bissau has shown that such supplementation provides little benefit and may be harmful to girls.

A total of 1717 neonates weighing <2500g at birth were randomised to vitamin A 25000 IU or placebo and to early or late BCG and followed up for 1 year. Overall, vitamin A supplementation was associated with a nonsignificant 8% increase in mortality. In boys there was a nonsignificant 26% reduction and in girls a nonsignificant 42% increase in mortality with vitamin A compared with placebo. It is concluded that the introduction of a neonatal vitamin A supplementation policy in Guinea-Bissau would not be beneficial. Giving BCG early or late made no difference.

The beneficial effects of vitamin A supplementation late in infancy are not doubted.

Benn CS et al. Vitamin A supplementation and BCG vaccination at birth in low birthweight neonates: two by two factorial randomised controlled trial. *BMJ* 2010; 340: 636 (c1101); Prentice AM. Vitamin A supplements and survival in children. *Ibid*: 607–8 (c977).

### Rapid testing for malaria in Ghana

Reports from East Africa have suggested that rapid tests for malaria, although sensitive and specific, do little to alter treatment rates. A report from Ghana has shown that rapid testing significantly reduces rates of unnecessary antimalarial treatment in places where microscopy is not used.

The study included 7263 children and adults with suspected malaria at four clinics, only one of which used microscopy to

diagnose malaria, the other three relying on clinical diagnosis. Patients were randomised to either rapid testing or the usual method of diagnosis. All patients had microscopy for the research trial but the results were not disclosed to clinicians. In the clinic with microscopy facilities rapid testing did not have a significant effect on the rate of treatment for malaria among patients with negative research slides (51.6% in the rapid testing group vs 55.0% in the routine microscopy group). In the clinics without routine microscopy, however, rapid testing reduced the rate of antimalarial treatment in patients with negative research slides from 90.1% to 53.9%. In the clinics without routine microscopy, malaria was treated correctly in 65.3% of patients in the rapid testing group and in 42.0% of patients in the clinical diagnosis-only group. Among patients with negative research slides, rapid testing increased the use of antibiotics from 25.9% to 34.5% in clinics without routine microscopy.

The use of rapid diagnostic testing led to better use of antimalarials and antibiotics in clinics that routinely relied on clinical diagnosis of malaria.

Ansah EK et al. Rapid testing for malaria in settings where microscopy is available and peripheral clinics where only presumptive treatment is available: a randomised controlled trial in Ghana. *BMJ* 2010; 340: 635 (C930).

## Diabetes

### Statins and diabetes risk

Data from large clinical trials have provided conflicting evidence as to whether statin treatment increases or reduces the risk of developing diabetes. Now a meta-analysis has shown a small increase in this risk.

The analysis included 13 statin trials (91 140 patients). Over a mean period of 4 years, diabetes developed in 2226 subjects on statin treatment and 2052 controls.

Overall there was a significant 9% increase in risk of diabetes with statin therapy. A total of 255 patients would have to take a statin for 4 years for there to be one extra case of diabetes.

It is concluded that the low absolute risk and the proved benefits of statin therapy indicate that the uses of statins need not change.

Sattar N et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010; 375: 735–42; Cannon CP. Balancing the benefits of statins versus a new risk – diabetes. *Ibid*: 700–1 (comment).

### Closed-loop insulin delivery for children and adolescents

Tight diabetic control reduces the risks of long-term diabetic complications but entails an increased risk of hypoglycaemia. A series of studies in Cambridge have shown that overnight use of a closed-loop insulin delivery system might reduce the risk of nocturnal hypoglycaemia in children and adolescents with difficult-to-manage type 1 diabetes.

The trials included 17 patients aged 5–18 years who were already being treated with continuous subcutaneous insulin via a pump. There were three separate trials, each with a crossover design with two sessions 1–5 weeks apart. Two studies compared closed-loop delivery with usual s.c. continuous insulin, one study with prior exercise. In the third study all patients received closed-loop delivery and randomisation was to a rapidly or a slowly absorbed meal. Each of the studies ran from 8.00 p.m. to 8.00 a.m. During closed-loop delivery nights an s.c. glucose sensor was fitted and a nurse adjusted the insulin infusion rate every 15 minutes according to a control algorithm.

Overall, in the three studies, times in the target range for plasma glucose (3.91–8.00 mmol/L) and times with low plasma glucose (3.90 mmol/L or less) were similar in the two groups. An analysis of pooled data showed that the closed-loop groups spent more time in the target range and less in the low range compared with the control groups. No patient on closed-loop delivery had a plasma glucose <3.0 mmol/L but this occurred nine times in the control groups.

Use of closed-loop systems could reduce the risk of nocturnal hypoglycaemia. The next step towards an 'artificial pancreas' will be to achieve good daytime and mealtime control.

Hovorka R et al. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. *Lancet* 2010; 375: 743–51; Renard E. Closed-loop insulin delivery: is the holy grail near? *Ibid*: 702–3 (comment).

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## Infection

### Management of urinary tract infection in women

Four successive papers in one issue of the BMJ have addressed issues in the management of urinary tract infection (UTI) in women.

In a general practice study in the south of England a total of 309 women aged 18–70 presenting with suspected uncomplicated UTI were randomised to one of five options: immediate empirical antibiotics; empirical antibiotics delayed by 48 hours; antibiotics according to symptom score (at least two of cloudy urine, smelly urine, nocturia, or dysuria); antibiotics with positive dipstick test for nitrite or leukocytes and blood; or antibiotics according to analysis of midstream urine (MSU). There were no significant differences between the groups in severity or duration of symptoms. Patients who delayed taking antibiotics had symptoms for 37% longer than those taking immediate antibiotics. It is concluded that there is no advantage in sending off an MSU routinely but a delayed prescription might reduce antibiotic use. A cost-effectiveness analysis favoured the immediate antibiotics and the dipstick testing groups. Dipstick testing with targeted antibiotics would be preferred if saving a day of moderately bad symptoms was valued at £10 or more. Many women preferred not to start antibiotics immediately and valued a delayed prescription but some questioned the delaying policy and needed more explanation.

In a further study by the same team 511 women had complete laboratory and clinical information. Severe symptoms lasted 3.3 days on average. Factors associated with longer duration of severe symptoms were antibiotic-resistant infections, non-prescription of antibiotics, symptoms of urethral syndrome, and

frequent somatic symptoms such as a history of cystitis, urinary frequency, and severe symptoms at baseline. Symptom duration was shorter when the doctor was thought to have a positive attitude about diagnosis and prognosis.

Little P et al. Effectiveness of five different approaches in management of urinary tract infection: randomised controlled trial. *BMJ* 2010; 340: 405 (c 199); Turner D et al. Cost effectiveness of management strategies for urinary tract infections: results from randomised controlled trial. *Ibid*: 406 (c346); Leydon GM et al. Women's views about management and cause of urinary tract infection: qualitative interview study. *Ibid*: 407 (c 279). Little P et al. Presentation pattern and natural course of severe symptoms, and role of antibiotics and antibiotic resistance among patients presenting with suspected uncomplicated urinary tract infection in primary care: observational study. *Ibid*: 408 (b 5633); Mangin D. Urinary tract infection in primary care. *Ibid*: 373–4 (c 657) (editorial).

## Surgery

### Sutures vs staples in orthopaedics

Both metal staples and nylon sutures are used to close skin wounds in orthopaedic surgery. A meta-analysis of published and unpublished studies has shown that the use of staples is associated with a three-fold increase in risk of infection. The analysis included six studies (683 patients). Wound closure was with sutures in 332 cases and with staples in 351. There was a 3.8-fold increase in risk of superficial wound infection with staples. After hip surgery this increase in risk was 4.8-fold.

Using staples rather than sutures to close the skin significantly increases the risk of superficial wound infection after orthopaedic surgery.

Smith TO et al. Sutures versus staples for skin closure in orthopaedic surgery. *BMJ* 2010; 340: 747 (c1199); Singh BI, McGarvey C. Staples for skin closure in surgery. *Ibid*: 719–20 (c403) (editorial).

### Carotid stenting vs endarterectomy for symptomatic carotid stenosis

Endarterectomy and stenting are possible treatments for symptomatic carotid stenosis but the results of trials have tended to favour endarterectomy. The results of an interim analysis of another trial have again shown better outcomes with endarterectomy.

The trial, at 50 centres in Europe, Australia, New Zealand, and Canada, included 1710 patients with recently symptomatic carotid stenosis who were randomised to stenting or endarterectomy. Within 120 days of randomisation, disabling stroke or death occurred in

4.0% (stenting) vs 3.2% (endarterectomy), a nonsignificant difference. The incidence of stroke, death, or procedural myocardial infarction was significantly greater in the stenting group (8.5% vs 5.2%) as was the risk of any stroke (65 events vs 35) and death from any cause (19 deaths vs 7). Of seven procedural myocardial infarctions the three in the stenting group were all fatal and the four in the endarterectomy group were all nonfatal. Cranial nerve palsy occurred in 1 patient in the stenting group and 45 in the endarterectomy group and haematomas occurred in 31 vs 50 patients. Follow-up is continuing.

Carotid endarterectomy remains the treatment of choice for patients suitable for surgery.

International Carotid Stenting Study investigators. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled study. *Lancet* 2010; 375: 985–97; Rothwell PM. Carotid stenting: more risky than endarterectomy and often no better than medical treatment alone. *Ibid*: 957–9 (comment).

## AIDS

### Screening for and diagnosis of tuberculosis in HIV-infected people: an algorithm

The World Health Organization recommends routine and regular screening for tuberculosis in people diagnosed with HIV infection. The methodology of this screening is, however, debated. A multi-centre study in Cambodia, Thailand, and Vietnam has given rise to an algorithm for tuberculosis screening and diagnosis. The study included 1748 patients with as yet untreated HIV infection. Each patient provided three sputum samples and one sample each of urine, stool and blood for mycobacterial culture. Lymph node aspirate was cultured from patients with lymphadenopathy. Patients underwent a standard clinical assessment with chest X-ray, complete blood count, and CD4+ cell count. A diagnosis of tuberculosis was made in 267 patients (15%) with a median CD4+ cell count of 242 per cu.mm. A history of a cough lasting 2 or 3 weeks in the last 4 weeks was obtained in 22–33% of cases of tuberculosis. A history of cough of any duration, fever of any duration, or night sweats for 3 or more weeks in the last 4 weeks was 93% sensitive and 36% specific for tuberculosis. A total of 249 (21%) of the 1199 patients with positive screening symp-

toms had tuberculosis. Among the 1199 patients, 1086 had two negative smears and 151 (14%) of these 1086 had tuberculosis. Among the 113 with at least one positive sputum smear (group 1) 98 (87%) had tuberculosis.

It is suggested that group 1 patients should have immediate treatment for tuberculosis. Among the 1086 patients with negative smears 250 had an abnormal chest X-ray (group 2) and 83 (33%) of those 250 had tuberculosis. Among the 836 patients with a normal chest X-ray 558 had a CD4+ count <350 cells per cu.mm (group 3) and 55 (10%) of the 558 had tuberculosis. It is suggested that clinical judgement should be used to decide which of patients in groups 2 and 3 should receive immediate antituberculosis treatment. All should have mycobacterial culture. For patients in group 4 (positive screening symptoms, negative smears, normal chest X-ray, CD4+ count at least 350 cells per cu.mm), optimum management is unclear. Reevaluation later might be the best (but unproved) policy. The algorithm divides patients initially into two groups by symptoms: an at-risk group (21% risk) and a low-risk group (3% risk). The at risk group is then further divided into groups 1, 2, 3, and 4 as defined above on the basis of sputum smears, chest X-ray, and CD4+ cell count. Group 1 patients should almost all have immediate antituberculosis treatment. For groups 2 and 3 immediate treatment will depend on clinical judgement. For group 4 there is uncertainty about the best management. They might simply be followed up later but the effectiveness of such a strategy is not known. Cain KP et al. An algorithm for tuberculosis screening and diagnosis in people with HIV. *NEJM* 2010; 362: 707–16.

### Poor HIV services for injecting drug users worldwide

Around the world there are 33 million people infected with HIV and between 800 000 and 6.6 million of them are injecting drug users. People infected with HIV through injecting drug use are able to infect others sexually. Interventions aimed at reducing HIV infection in injecting drug users include needle and syringe programmes, avoidance of equipment sharing, and treatments for drug addiction.

Antiretroviral treatment and provision of condoms might reduce HIV spread. Other interventions aimed at injecting drug users include HIV testing and counselling, education, treatment and preven-

tion of hepatitis, and treatment and prevention of tuberculosis. The worldwide provision of services for injecting drug users has been the subject of a systematic review.

In 2009, needle and syringe programmes (NSPs) were active in 82 countries, opioid substitution therapy (OST) in 70, and both in 66. NSPs were most active in Australia and least active in Latin America, the Caribbean, the Middle East, north Africa, and sub-Saharan Africa. OST provision was high in Western Europe and low in central Asia, Latin America, and sub-Saharan Africa. Antiretroviral therapy was readily available in Europe but not in Chile, Kenya, Pakistan, Russia, and Uzbekistan. Worldwide, provision of services for injecting drug users is inadequate.

Mathers BM et al. HIV prevention, treatment, and care services for people who inject drugs: systematic review of global, regional, and national coverage. *Lancet* 2010; 375: 1014–28; Des Jarlais DC et al. Increasing HIV prevention and care for injecting drug users. *Ibid*: 961–3 (comment).

### Co-trimoxazole prophylaxis for HIV-infected adults in Africa

WHO recommends co-trimoxazole prophylaxis for all HIV-infected symptomatic adults with CD4 counts <350 cells per  $\mu$ L but it has been used infrequently. Data from the Development of Anti-Retroviral Therapy in Africa (DART) trial in Uganda and Zimbabwe have strongly supported the use of co-trimoxazole prophylaxis for patients beginning antiretroviral therapy (ART)

In the DART trial, co-trimoxazole prophylaxis was used only at the clinician's discretion. The trial included 3179 patients about to start ART and with CD4 counts <200 cells per  $\mu$ L. There were 14214 person-years of follow-up and 8128 person-years (57%) on co-trimoxazole. Mortality was significantly reduced by 35% with current prophylaxis. On ART, mortality was reduced substantially in the first 12 weeks with a sustained effect up to 72 weeks but no detectable effect after than. Co-trimoxazole prophylaxis reduced the frequency of malaria but had no effect on the incidence of WHO stage 4 events, CD4 cell counts, or BMI.

Co-trimoxazole prophylaxis should be provided for at least 72 weeks for adults starting ART in Africa.

Walker AS et al. Daily co-trimoxazole prophylaxis in severely immunosuppressed HIV-infected adults in Africa started on combination antiretroviral therapy: an observational analysis of the DART cohort. *Lancet* 2010; 375: 1278–86; Anglaret X, Eholie S. Co-trimoxazole, cART, and non-AIDS infectious diseases. *Ibid*: 1231–3 (comment).