

## General

### Compression stockings for the prevention of post-thrombotic syndrome

Post-thrombotic syndrome (PTS) is a chronic disorder that develops in 25-50% of patients following deep vein thrombosis (DVT). PTS treatment is often ineffective and consequently prevention is paramount. Therefore, it has been suggested that elastic compression stockings (ECS) may reduce venous hypertension and reflux, and thereby prevent PTS.

A North American randomised trial assigned patients with a symptomatic, proximal DVT to receive either ECS (n=410) or placebo stockings (n=396). Patients were then monitored and the cumulative incidence of those diagnosed with PTS from six to 24 months was recorded from each group.

The cumulative incidence of PTS in the ECS group was 14.2% in the active ESC group versus 12.7% in the placebo group, yielding a non-significant hazard ratio of 1.13.

Elastic compression stockings did not prevent PTS after a first proximal DVT. Kahn S, Shapiro S, Wells P, Rodger M, Kovacs M, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. *Lancet*. 2014;383:880-8.

### Acetylcysteine treatment regimens for paracetamol poisoning

Paracetamol (acetaminophen) overdose is common worldwide and a frequent cause of acute liver failure. Intravenous acetylcysteine is the mainstay of paracetamol poisoning treatment, but the standard regimen is complex, associated with frequent adverse effects, and therefore results in regular treatment interruption.

A recent randomised trial assessed the adverse effect profile of the standard intravenous acetylcysteine regimen (20.25 hour duration) against a shorter (12 hour) modified protocol. The primary outcome measured the absence of vomiting, retching or need for rescue antiemetic treatment at two hours.

The primary outcome was reported in 39 of 108 patients in the shorter modified protocol in comparison with 71 of 109 allocated to the standard regimen (significant adjusted odds ratio (OR), 0.26). Severe anaphylactoid reactions were recorded in five patients in the modified protocol versus 31 in the standard regimen.

The shorter 12-hour acetylcysteine regimen resulted in reduced vomiting and anaphylactoid reactions in addition to less frequent treatment interruption.

Bateman N, Dear J, Thanacoody R, Thomas S, Edleston M, et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial. *Lancet*. 2014;383:697-704.

### Health outcomes and vitamin D

The association between vitamin D concentrations and numerous health outcomes has been extensively investigated over the years. Evidence has suggested vitamin D deficiency may be linked to metabolic disorders, skeletal and cardiovascular disease, and even cancer, but the research is frequently confusing and contradictory. Therefore, an umbrella review of 107 systematic reviews and meta-analyses of 161 observational studies and trials has investigated the effects of vitamin D concentration or supplementation in relation to 137 health outcomes.

Despite the large volume of research, no convincing evidence was found to clearly link the role of vitamin D to any health outcome. However, it is probable that vitamin D supplementation results in a decrease in dental caries in children, a decrease in parathyroid hormone in patients with chronic kidney disease requiring dialysis, and increased birth-weights at term.

No convincing evidence suggests a clear role of vitamin D in relation to health outcomes but associations with a selection of outcomes are probable.

Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis J. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. *BMJ*. 2014;348:2035.

### Urethral stone prediction score

Approximately one in 11 people in the United States will develop kidney stones at some point during their lifetime. Computed tomography (CT) is currently the first line imaging method for kidney stones but this involves exposure to high levels of radiation, and is often unnecessary as the majority of patients pass urethral stones spontaneously. Therefore a clinical prediction score (STONE) has been derived to predict the diagnosis of uncomplicated urethral stones.

Retrospective analysis of patient's records and CT scans were examined to identify the top five factors associated with urethral stones. These were then used to derive a scoring system that stratifies the presence of kidney stones as low, moderate, and high probability. The scoring system (ranging from 1-13)

was then validated prospectively on 491 participants. Amongst these patients, it was established that urethral stones were present in 9.2% of patients classified as low probability (score 0-5), 51.3% of the moderate probability group (6-9), and 88.6% of the high probability group (10-13). Amongst the high probability patients, important alternative findings were present in only 1.6% of patients.

The STONE score reliably predicts the presence of uncomplicated urethral stones.

Moore C, Bomann S, Daniels B, Luty S, Molinaro A, et al. Derivation and validation of a clinical prediction rule for uncomplicated ureteral stone—the STONE score: retrospective and prospective observational cohort studies. *BMJ*. 2014;348.

### Chronic kidney disease in sub-Saharan Africa

The combination of urbanisation, population ageing, and lifestyle changes has resulted in a continued increasing prevalence of non-communicable disease such as chronic kidney disease (CKD). The people of sub-Saharan Africa are especially vulnerable to kidney disease partly due to communicable diseases, including HIV and infectious glomerulonephritis, but little is known about the epidemiology of CKD in the region.

A systematic review and meta-analysis of 90 studies from across sub-Saharan Africa aimed to investigate the prevalence of CKD. The majority of studies were performed in urban areas, but no significant difference in prevalence was detected between urban and rural areas (12.4% vs 16.5% respectively). The overall prevalence was estimated to be 13.9%, half the studies estimates ranged from between 4 and 14%, and all but one country had a prevalence of less than 20%.

CKD is a substantial health burden that is set to increase across sub-Saharan Africa.

Stanifer J, Jing B, Tolan S, Helmke N, Mukerjee R, et al. The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Global Health*. 2014;2:174-81.

## Surgery

### Surgical site infections following ambulatory surgery

Surgical site infections (SSIs) are the most common healthcare-associated infection and can result in substantial morbidity. Ambulatory surgeries represent a substantial proportion of surgical healthcare but little is known about

infectious outcomes following ambulatory operations.

A retrospective analysis of 280 000 ambulatory surgical procedures collated from eight American states was performed in order to identify the rate of postsurgical acute care visits for clinically significant surgical site infections (CS-SSIs).

Postsurgical acute care visits relating to CS-SSIs occurred in 3.09 per 1000 ambulatory procedures at 14 days, and 4.84 per 1000 at 30 days. Two-thirds of all visits for CS-SSIs occurred within 14 days of surgery, and of those visits the vast majority involved inpatient treatment.

The rates of postsurgical visits for CS-SSIs were low but may represent a substantial number due to the large number of procedures.

Owens P, Barrett M, Raetzman S, Maggard-Gibbons M, and Steiner C. Surgical site infections following ambulatory surgery procedures. *JAMA*. 2014;311:709–16.

### Surgical safety checklists effects

The introduction of surgical safety checklists has been implemented worldwide to reduce surgical mortality and complication rates. However, the effects of mandatory adoption of safety checklists remain unclear.

A Canadian study compared the operative mortality and complication rates across 101 hospitals before and after checklists were adopted. Analysis of over 200 000 procedures revealed no significant reduction in risk of death after three months of checklist implementation. The adjusted risk of death was 0.71% before implementation, and 0.62% after (insignificant adjusted OR of 0.91). No significant reduction in odds ratio was seen in the rate of surgical complications (3.86% before implementation and 3.82% after).

Surgical safety checklists did not significantly reduce mortality or complications after surgery.

Urbach D, Govindarajan A, Saskin R, Wilton A, Baxter N. Introduction of Surgical Safety Checklists in Ontario, Canada. *NEJM*. 2014;370:1029–38.

### Surgical approaches for apical vaginal prolapse

Most surgery for pelvic organ prolapse is performed transvaginally with two approaches favoured by surgeons when correcting apical vaginal prolapse: sacrospinous ligament fixation (SSLF) and uterosacral ligament suspension (ULS). However, little is known about their relative safety or efficacy.

A randomised multicentre trial assigned women to receive either SSLF

(n=186) or ULS (n=188) approaches for apical vaginal prolapse. After two years, the two surgical approaches did not differ significantly for either success rates (ULS, 59.2% vs SSLF 60.5%; adjusted OR, 0.9), or serious adverse events rates (ULS, 16.5% vs SSLF, 16.7%; adjusted OR, 0.9).

Surgical success rates between the SSLF and ULF approaches did not differ after two years.

Barber M, Brubaker L, Burgio K, Richter H, Nygaard I, et al. Comparison of 2 transvaginal surgical approaches and perioperative behavioral therapy for apical vaginal prolapse: The optimal randomized trial. *JAMA*. 2014;311:1023–34.

## Cardiovascular

### Transcatheter aortic-valve replacement with a self-expanding prosthesis

Aortic stenosis is a serious disease that results in a poor prognosis after symptom onset. The condition can be managed using valve replacement by utilising conventional open heart surgery or transcatheter aortic-valve replacement (TAVR). Recently, a randomised multicentre trial assessed the safety and efficacy of TAVR as compared with surgical valve replacement in patients with severe aortic stenosis classified as increased surgical risk.

A total of 795 patients underwent randomisation to one of the two replacement strategies. The rate of death at one year was significantly lower in the surgical group compared with the TVAR with bioprosthesis (14.2% versus 19.1% respectively, absolute risk reduction of 4.9 percentage points).

In patients with severe aortic stenosis carrying an increased risk of surgery, TVAR with a self-expanding bioprosthesis was associated with a higher rate of survival at one year compared with patients undergoing surgical replacement.

Adams D, Popma J, Reardon M, Yakubov S, Coselli J, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *NEJM* 2014.

### Blood pressure in septic shock

Septic shock is characterised by arterial hypotension despite adequate fluid resuscitation. Guidelines recommend resuscitation with vasopressors to reverse hypotension and maintain a mean arterial pressure of at least 65 mmHg, however the optimal pressure target remains controversial.

A multicentre randomised trial investigated the effects of resuscitation on

mortality when a mean atrial pressure was maintained at a higher level of 80 to 85 mmHg (n=388) compared with a lower pressure of 65 to 70 mmHg (n=388). At 28 days a mortality rate of 36.6% was observed in the high target group versus 34.0% in the low target group. The hazard ratios calculated at 28 and 90 days were 1.07 and 1.04, respectively, both were insignificant.

A higher mean arterial pressure provided survival advantage compared with those patients with a lower arterial pressure.

Asfar P, Meziani F, Hamel J, Grelon F, Megarbane B, et al. High versus low blood-pressure target in patients with septic shock. *NEJM*. 2014.

### Renal artery denervation of resistant hypertension

Due to an ageing population and rising obesity, the prevalence of hypertension is increasing across the globe. Approximately 10% of these patients have treatment-resistant hypertension, and therefore, carry an increased risk of cardiovascular complications. Evidence has emerged from a number of small studies suggesting renal artery denervation may provide an alternative treatment for these patients.

A trial randomised 535 treatment-resistant hypertensive patients in a 2:1 ratio to undergo either renal denervation or sham procedure, respectively. The primary endpoint measured change in systolic blood pressure from baseline at six months.

The denervation group systolic blood pressure decreased by  $-14.13 \pm 23.93$  mmHg at 6 months in contrast to  $-11.74 \pm 25.94$  mmHg in the sham-procedure group, yielding an insignificant difference of minus 2.39 mmHg between the groups. In addition, no significant difference in 24-hour ambulatory systolic blood pressure was observed at the same time point.

Renal artery denervation did not significantly reduce systolic blood pressure at 6 months.

Bhatt D, Kandzari D, O'Neill W, D'Agostino R, Flack J, et al. A controlled trial of renal denervation for resistant hypertension. *NEJM*. 2014.

## Obs & Gyn

### Invasive *Haemophilus influenzae* in pregnancy

Unencapsulated *Haemophilus influenzae* frequently causes non-invasive upper respiratory tract infections, but can also cause invasive disease. Studies have

suggested that pregnant women may have increased risk of unencapsulated *H. influenzae*, and therefore, a study conducted across England aimed to assess the association between invasive *H. influenzae* and pregnancy outcomes

A total of 44% of the 171 women (median age, 28 years) with unencapsulated *H. influenzae* were pregnant at the time of infection, most of whom were previously healthy. The incidence rate among pregnant women for unencapsulated

*H. influenzae* was 2.98 per 100 000 woman-years, 17 times greater than non-pregnant women. Infection during the first 24 weeks of pregnancy was associated with foetal loss in 94% of cases and extremely premature birth (6% of the women). Infection during the second half of pregnancy was associated with premature birth in 30% of cases, whilst 7% of women had stillbirths.

Pregnancy was associated with greater risk of invasive *H. influenzae*, which in turn is linked to poor pregnancy outcomes.

Collins S, Ramsay M, Slack M, Campbell H, Flynn S, et al. Risk of invasive *Haemophilus influenzae* infection during pregnancy and association with adverse fetal outcomes. *JAMA*. 2014;311:1125–32.

### Maternal mortality in adolescents

Each year 16 million women aged 15–19 years become first-time mothers. Although mortality risk amongst adolescent mothers has not been recently accurately quantified, older research suggests that adolescent mothers are more likely to die from maternal causes than mothers in their early twenties.

Data collated from 144 countries were analysed to reveal that adolescents were at a marginally increased risk of mortality amongst adolescents compared with women aged 20–24 (maternal mortality rate (MMR) 260 vs 190 maternal deaths per 100 000 livebirths, respectively), but women with the highest risk were aged over 30 years. Highest MMR ratios were calculated in Nigeria, India, and Ethiopia, although considerable variation was observed across many countries. Furthermore, over one third of the countries had lower adolescent mortality compared with women in their 20s.

Maternal mortality rates were increased amongst adolescents, but this mortality risk is less than originally estimated.

Nove A, Matthews Z, Neal S, and Camacho A. Maternal mortality in adolescents compared with women of other ages: evidence from 144 countries. *Lancet Global Health*. 2014;2:155–64.

### Hyperimmune globulin for congenital cytomegalovirus prevention

Congenital infection with human cytomegalovirus (CMV) occurs in 0.6% of births in the United States and can cause major morbidity and mortality. However, evidence from an uncontrolled study found administration of CMV-specific hyperimmune globulin significantly reduced intrauterine transmission rates.

A placebo-controlled, randomised trial assessed the efficacy and safety of hyperimmune globulin in a cohort of 124 pregnant women with CMV infection between 5 and 26 weeks of gestation.

The rate of congenital infection was 30% amongst the hyperimmune globulin group versus 44% in the placebo group, yielding an insignificant difference of 14 percentage points. Although congenital infection rates were similar between the two groups, the number of obstetrical adverse events were higher in the hyperimmune globulin group (13%), including 11 serious events, compared with 2% in the placebo group.

Treatment with hyperimmune globulin did not significantly reduce congenital CMV infection.

Revello M, Lazzarotto T, Guerra B, Spinillo A, Ferrazzi E, et al. A randomized trial of hyperimmune globulin to prevent congenital cytomegalovirus. *NEJM*. 2014;370:1316–26.

## Paediatrics

### Acute otorrhea treatment in children with tympanostomy tubes

The insertion of tympanostomy tubes can result in incidence rates of acute otorrhea ranging from 25% to 75%. Treatment guidance for acute otorrhea is based upon limited evidence from small studies, so therefore, a recent trial assessed the relative efficacy of glucocorticoid-antibiotic eardrops (hydrocortisone-bacitracin-colistin), oral antibiotics (amoxicillin-clavulanate), and initial observation in children with acute otorrhea.

A total of 230 children aged one to ten years were randomly assigned 1:1:1 to each of the three treatments. A total of 5% of children treated with the antibiotic-glucocorticoid combination had otorrhea at two weeks, which was significantly less than those treated with oral antibiotics (44% had otorrhea at 14 days), and 55% in those receiving initial observation. The duration of initial episode was four days in the antibiotic-glucocorticoid group which was calculated

as significantly shorter than the five day duration calculated in oral antibiotic and 12 days in the observation group.

Antibiotic-glucocorticoid eardrop treatment was more effective than oral antibiotics and initial observation.

Van Dongen T, van der Heijden G, Venekamp R, Rovers M, and Schilder A. A trial of treatment for acute otorrhea in children with tympanostomy tubes. *NEJM*. 2014;370:723–33.

### Causes of fever in Tanzanian children

As the number of malarial cases recedes across much of the African continent, there is increasing awareness of other infectious diseases causing acute febrile episodes requiring identification and appropriate treatment.

A study of 1000 Tanzanian children assessed the causes of fever and the relative burden of bacterial, viral and parasitic pathogens in both rural and urban settings. The most common cause of acute febrile fever was acute respiratory tract infection (62% of cases). Systemic bacterial, viral or parasitic infections (excluding typhoid and malaria) were diagnosed in 13% of children, 12% were caused by nasopharyngeal viral infections, whilst both malaria and gastroenteritis fevers were found in around 10% of the children (22% of children had multiple diagnoses). A total of 71% of the children were diagnosed with a viral disease, 22% had a bacterial disease, and 11% had a parasitic disease.

Evidence of a viral process was found more commonly than evidence of a bacterial or parasitic process.

D'Acremont V, Kilowoko M, Kyungu E, Philipina S, Sangu W, et al. Beyond malaria — causes of fever in outpatient Tanzanian children. *NEJM*. 2014;370:809–17.

### Probiotics in infant colic

Infant colic is characterised by crying or fussing from an unknown cause and is estimated to affect around 20% of infants. Currently, no single effective treatment for the condition exists, and therefore management involves support and reassurance. However, recent evidence suggests that probiotics (live microorganisms that confer health benefits) provide an effective treatment.

An Australian placebo-controlled trial tested the efficacy of administering *Lactobacillus reuteri* for the treatment of infant colic in infants (aged less than three months). The primary outcome measured the daily duration of crying and fussing at one month.

A total of 85 infants were assigned to receive the probiotic and 82 to the

placebo for a total of 28 days. Crying and fussing decreased steadily in both groups, however at one month the probiotic group cried or fussed significantly more than infants in the placebo group.

*Lactobacillus reuteri* was not effective at treating infant colic.

Sung V, Hiscock H, Tang M, Mensah F, Nation M, et al. Treating infant colic with the probiotic *Lactobacillus reuteri*: double blind, placebo controlled randomised trial. *BMJ*. 2014;348:2107.

## Infection

### Novel Enterovirus 71 vaccine

Enterovirus 71 (EV71) not associated with poliomyelitis is a major cause of hand, foot, and mouth disease, or herpangina worldwide. A phase three clinical trial in China evaluated the efficacy and safety of a novel EV71 vaccine.

A total of 10 007 children aged 6-35 months were randomly assigned to receive either two intramuscular doses of either EV71 vaccine or a placebo 28 days apart.

One year after the administration of the vaccine, 0.3% of the children (13 of 5041) versus 2.1% of the placebo (106 of 5028) had EV71-associated disease. The estimated 94.8% efficacy of the vaccine against EV71-associated hand, foot, and mouth disease, or herpangina was highly significant. No children in the vaccine group were hospitalised compared with 24 hospitalisations in the placebo group, of which eight suffered neurological complications.

The EV71 vaccine is effective in the prevention of hand, foot, and mouth disease, or herpangina in infants and young children.

Zhu F, Xu W, Xia J, Liang Z, Liu Y, et al. Efficacy, safety, and immunogenicity of an enterovirus 71 vaccine in China. *NEJM*. 2014;370:818-28.

### Albumin replacement for sepsis

Due to the ability of albumin to provide adequate oncotic pressure and intravascular volume, it is frequently used to treat patients with severe sepsis or septic shock. However, its efficacy has never been fully established.

A multicentre randomised trial assigned 1818 patients to receive either 20% albumin in combination with crystalloid solution or crystalloid solution alone. The outcomes measured mortality at 28 and 90 days.

During the first week patients in the albumin group had both significantly higher mean arterial pressure and lower net fluid balance. However, the mortal-

ity between the albumin and crystalloid groups at both 28 and 90 days did not differ significantly. At 28 days the mortality rate was 31.8% in the albumin group and 32.0% in the crystalloid group (relative risk (RR), 1.00), respectively compared with 41.1% and 43.6% at 90 days, (RR, 0.94).

Albumin replacement in severe sepsis did not improve survival rates at 28 or 90 days.

Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, et al. Albumin replacement in patients with severe sepsis or septic shock. *NEJM*. 2014.

### Patient outcomes in drug-resistant tuberculosis

In 2010, an estimated 650 000 (5.4%) of tuberculosis cases were estimated to be drug-resistant, of which 5-10% were classified as extensively drug-resistant (XDR). A prospective study of XDR tuberculosis cases from South Africa aimed to establish the long-term treatment related outcomes amongst these patients.

Before enrolment, all patients were classified as XDR having received a median of eight drugs and were treated empirically as inpatients. At 60 months, 12 patients (11%) had been cured or reached treatment completion, 73% had died, and 10% had failed treatment. A total of 42% of patients discharged from hospital had failed treatment, whilst 58% had achieved sputum culture conversion. Patients who failed treatment and were discharged had a median survival of 20 months. Net culture conversion was a strong predictor of survival, as was treatment with clofazimine.

Long-term outcomes of XDR are poor, irrespective of HIV status.

Pietersen E, Ignatius E, Streicher E, Mastrapa B, Padanilam X, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. *Lancet*. 2014;383:1230-9.

### Oxantel pamoate-albendazole for *Trichuris trichiura* infection

Soil transmitted helminthiasis caused by *Ascaris lumbricoides*, hookworm and

*Trichuris trichiura*, are estimated to infect over one billion people worldwide. Treatment comprising of albendazole or mebendazole are the typical agents used against parasitic-worm infections, but both show low efficacy against *T. trichiura*. Albendazole is the drug of choice against hookworm.

A randomised trial in Tanzania recruited 458 *T. trichiura* infected children aged 6-14 and were then assigned to one of four treatment regimens: oxantel pamoate (20mg/kg), plus albendazole (400mg) administered on consecutive days; a single dose of oxantel pamoate (20mg/kg); a single 400mg albendazole dose; or mebendazole at a single dose of 500mg.

The cure rate of *T. trichiura* was significantly higher with oxantel pamoate-albendazole than with mebendazole (31.2% vs. 11.8%), as was the egg-reduction rate (96.0% vs. 75.0%). The cure rate was significantly lower in albendazole-treated children (2.6%) than in mebendazole treated. Oxantel pamoate-albendazole cure rates were 51.4% and 94.4% for hookworm and *A. lumbricoides*, respectively.

Oxantel pamoate-albendazole results in higher cure rates and egg-reduction rates than the standard treatment.

Speich B, Ame S, Ali S, Alles R, Huwyler J, et al. Oxantel pamoate-albendazole for trichuris trichiura infection. *NEJM*. 2014;370:610-20.

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