Background: Early mobilisation after stroke is thought to contribute to the effects of stroke-unit care; however, the intervention is poorly defined and not underpinned by strong evidence. We aimed to compare the effectiveness of frequent, higher dose, very early mobilisation with usual care after stroke.

Methods: We did this parallel-group, single-blind, randomised controlled trial at 56 acute stroke units in five countries. Patients (aged > 18 years) with ischaemic or haemorrhagic stroke, first or recurrent who met physiological criteria were randomly assigned (1:1), via a web-based computer generated block randomisation procedure (block size of six), to receive usual stroke-unit care alone or very early mobilisation in addition to usual care. Treatment with recombinant tissue plasminogen activator was allowed. Randomisation was stratified by study site and stroke severity. Patients, outcome assessors, and investigators involved in trial and data management were masked to treatment allocation. The primary outcome was a favourable outcome 3 months after stroke, defined as a modified Rankin Scale score of 0-2. We did analysis on an intention-to-treat basis. The trial is registered with the Australian New Zealand Clinical Trials Registry.

Findings: Between July 18, 2006, and Oct 16, 2014, we randomly assigned 2104 patients to receive either very early mobilisation (n=1054) or usual care (n=1050); 2083 (99%) patients were included in the 3 month follow-up assessment. 965 (92%) patients were mobilised within 24 h in the very early mobilisation group compared with 623 (59%) patients in the usual care group. Fewer patients in the very early mobilisation group had a favourable outcome than those in the usual care group (n=480 [46%] vs n=525 [50%]; adjusted odds ratio [OR] 0.73, 95% CI : 0.59-0.90; p=0.004), 88 (8%) patients died in the very early mobilisation group compared with 72 (7%) patients in the usual care group (OR 1.34, 95% CI 0.93-1.93, p=0.113), 201 (19%) patients in the very early mobilisation group and 208 (20%) of those in the usual care group had a non-fatal serious adverse event, with no reduction in immobility-related complications with very early mobilisation.

Interpretation: First mobilisation took place within 24 h for most patients in this trial. The higher dose, very early mobilisation protocol was associated with a reduction in the odds of a favourable outcome at 3 months. Early mobilisation after stroke is recommended in many clinical practice guidelines worldwide and our findings should affect clinical practice by refining present guidelines; however, clinical recommendations should be informed by future analyses of dose-response associations.

A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management
Pt-Sunyer X, Astrup A

Background: Obesity is a chronic disease with serious health consequences, but weight loss is difficult to maintain through lifestyle intervention alone. Liraglutide, a glucagon-like peptide-1 analogue, has been shown to have potential benefit for weight management at a once-daily dose of 3.0 mg, injected subcutaneously.

Methods: We conducted a 56-week, double-blind trial involving 3731 patients who did not have type 2 diabetes and who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of at least 30 or a BMI of at least 27 if they had treated or untreated dyslipidemia or hypertension. We randomly assigned patients in a 2:1 ratio to receive once-daily subcutaneous injections of liraglutide at a dose of 3.0 mg (2487 patients) or placebo (1244 patients); both groups received counseling on lifestyle modification. The coprimary end points were the change in body weight and the proportions of patients losing at least 5% and more than 10% of their initial body weight.

Results: At baseline, the mean (±SD) age of the patients was 45.1±12.0 years, the mean weight was 106.2±21.4 kg, and the mean BMI was 38.3±6.4; a total of 78.9% of the patients were women and 61.2% had prediabetes. At week 56, patients in the liraglutide group had lost a mean of 8.4±7.3 kg of body weight, and those in the placebo group had lost a mean of 2.8±6.5 kg (a difference of -5.6 kg; 95% confidence interval, -6.0 to -5.1; P<0.001, with last-observation carried-forward imputation). A total of 63.2% of the patients in the liraglutide group as compared with 27.1% in the placebo group lost at least 5% of their body weight (P<0.001), and 33. 1 % and 10.6%, respectively, lost more than 10% of their body weight (P<0.001). The most frequently reported adverse events with liraglutide were mild or moderate nausea and diarrhea. Serious events occurred in 6.2% of the patients in the liraglutide group and in 5.0% of the patients in the placebo group.
Conclusions: In this study, 3.0 mg of liraglutide, as an adjunct to diet and exercise, was associated with reduced body weight and improved metabolic control.

**Tenofovir Gel for the Prevention of Herpes Simplex Virus Type 2 Infection**

Salim S, Karim A
Karim A, Kharsany ABM, et al
N Engl J Med 2015; 373:530-539

**Background:** Globally, herpes simplex virus type 2 (HSV-2) infection is the most common cause of genital ulcer disease. Effective prevention strategies for HSV-2 infection are needed to achieve the goals of the World Health Organization global strategy for the prevention and control of sexually transmitted infections.

**Methods:** We assessed the effectiveness of pericoital tenofovir gel, an antiviral microbicide, in preventing HSV-2 acquisition in a subgroup of 422 HSV-2-negative women enrolled in the Centre for the AIDS Programme of Research in South Africa a double-blind, randomized, placebo-controlled trial. Incident HSV-2 cases were identified by evidence of seroconversion on an HSV-2 IgG enzyme-linked immunosorbent assay between study enrollment and exit. A confirmatory analysis was performed by Western blot testing.

**Results:** The HSV-2 incidence rate was 10.2 cases per 100 person-years (95% confidence interval [CI], 6.8 to 14.7) among 202 women assigned to tenofovir gel, as compared with 21.0 cases per 100 person-years (95% CI, 16.0 to 27.2) among 222 women assigned to placebo gel (incidence rate ratio, 0.49; 95% CI, 0.30 to 0.77; P=0.003). The HSV-2 incidence rate among the 25 women with vaginal tenofovir concentrations of 10,000 mg per milliliter or more was 5.7 cases per 100 person-years, as compared with 15.5 cases per 100 person-years among the 103 women with no detectable vaginal tenofovir (incidence rate ratio, 0.37; 95% CI, 0.04 to 1.51; P=0.14). As confirmed by Western blot testing, there were 16 HSV-2 seroconversions among women assigned to tenofovir gel as compared with 36 among those assigned to the placebo gel (incidence rate ratio, 0.45; 95% CI, 0.23 to 0.82; P=0.005).

**Conclusions:** In this study in South Africa, pericoital application of tenofovir gel reduced HSV-2 acquisition in women.

**Antiepileptic drug treatment of rolandic epilepsy and Panayiotopoulos syndrome: clinical practice survey and clinical trial feasibility**

Mellish LC, Dunkley C, Ferre CD, et al

**Background:** The evidence base for management of childhood epilepsy is poor, especially for the most common specific syndromes such as rolandic epilepsy (RE) and Panayiotopoulos syndrome (PS). Considerable international variation in management and controversy about non-treatment indicate the need for high quality randomised controlled trials (RCT). The aim of this study is, therefore, to describe current UK practice and explore the feasibility of different RCT designs for RE and PS.

**Methods:** We conducted an online survey of 590-UK paediatricians who treat epilepsy. Thirty-two questions covered annual caseload, investigation and management practice, factors influencing treatment, antiepileptic drug preferences and hypothetical trial design preferences.

**Results:** 132 responded (22%): 81% were paediatricians and 95% at consultant seniority. We estimated, annually, 751 new RE cases and 233 PS cases. Electroencephalography (EEG) is requested at least half the time in approximately 70% of cases; MRI brain at least half the time in 40%-65% cases and neuropsychological evaluation in 7%-8%. Clinicians reported non-treatment in 40% main reasons were low frequency of seizures and parent child preferences. Carbamazepine is the preferred older, and levetiracetam the preferred newer, RCT arm. Approximately one-half considered active and placebo designs acceptable, choosing seizures as primary and cognitive/behavioural measures as secondary outcomes.

**Conclusions:** Management among respondents is broadly in line with national guidance, although with possible overuse of brain imaging and under use of EEG and neuropsychological assessments. A large proportion of patients in the UK remains untreated, and clinicians seem amenable to a range of RCT designs, with carbamazepine and levetiracetam the preferred active drugs.

**Reducing hospital-acquired infections and improving the rational use of antibiotics in a developing country: an effectiveness study**

Murni IK, Duke T, Kinney S, et al
Arch Dis Child 2015; 100: 454-459

**Background:** Prevention of hospital-acquired infections (HAI) is central to providing safe and high quality healthcare. Transmission of infection between patients by health workers, and the irrational use of antibiotics have been identified as preventable aetiological factors for HAI. Few studies have addressed this in developing countries.

**Aims:** To implement a multifaceted infection control and antibiotic stewardship programme and evaluate its effectiveness on HAIIs and antibiotic use.
Methods: A before and after study was conducted over 27 months in a teaching hospital in Indonesia. All children admitted to the paediatric intensive care unit and paediatric wards were observed daily. Assessment of HAIs was made based on the criteria from the Centers for Disease Control and Prevention. The multifaceted intervention consisted of a hand hygiene campaign, antibiotic stewardship (using the WHO Pocket Book of Hospital Care for Children guidelines as standards of antibiotic prescribing for community-acquired infections), and other elementary infection control practices. Data were collected using an identical method in the preintervention and postintervention periods.

Results: We observed a major reduction in HAIs, from 22.6% (277/1227 patients) in the preintervention period to 8.6% (123/1419 patients) in the postintervention period (relative risk [RR] 95% CI) 0.38 (0.31 to 0.46). Inappropriate antibiotic use declined from 43% (336 of 780 patients who were prescribed antibiotics) to 20.6% (182 of 882 patients) (RR 0.46 (0.40 to 0.55)). Hand hygiene compliance increased from 18.9% (319/1690) to 62.9% (1125/1789) (RR 3.33 (2.99 to 3.70). In hospital mortality decreased from 10.4% (127/1227) to 8% (114/1419) (RR 0.78 (0.61 to 0.97)).

Conclusions: Multifaceted infection control interventions are effective in reducing HAI rates, improving the rational use of antibiotics, increasing hand hygiene compliance, and may reduce mortality in hospitalised children in developing countries.

Liver regeneration following experimental major hepatectomy with choledochojejunostomy
Takagi T, Yokoyama Y, Kokuryo T, et al
BJS 2015 : 102 : 1410-7

Background: Surgical treatment for perihilar cholangiocarcinoma frequently involves hepatectomy and extrahepatic bile duct resection with a choledochojejunostomy (CJ). Cholangitis owing to bilioenteric anastomosis is a common complication. The impact of CJ or regurgitating cholangitis on the liver regeneration process after major hepatectomy is unknown.

Methods: Rats underwent 70 per cent hepatectomy (Hx group) or hepatectomy with CJ (Hx + CJ group). The intrahepatic inflammatory response, hepatic regeneration rate, and expression of regeneration-associated genes in the liver and blood were compared between these two groups.

Results: Levels of hepatobiliary markers in the blood were significantly higher 4 and 7 days after operation in the Hx + CJ group than the Hx group. Intrahepatic expression of inflammation-associated genes, such as interleukin 6 and tumour necrosis factor a, was also significantly higher in the Hx + CJ group on days 4 and 7. A progressive periportal inflammatory response was identified in the Hx + CJ group by histological examination. The hepatic regeneration rate was significantly lower in the Hx + CJ group than in the Hx group on day 2 (mean(s.d.) 14.2(6.3) versus 21.4(2.6) per cent; P = 0.013) and day 4 (32.4(5.3) versus 41.3(4.4) per cent; P = 0.004). Gene expression levels of hepatic regeneration-promoting factors such as hepatocyte growth factor were significantly lower in the Hx + CJ group than the Hx group on day 1.

Conclusion: CJ perturbs early liver regeneration after hepatectomy. An excessive inflammatory response in the liver and suppression of liver regeneration-associated factors may play a role.

Patients with perihilar cholangiocarcinoma may need major hepatectomy with extrahepatic bile duct resection and choledochojejunostomy. This carries a substantial risk of postoperative complications including liver failure. A rat model of partial hepatectomy with choledochojejunostomy was established. The molecular mechanisms underlying liver regeneration, and perturbation of this process by duodenobiliary reflux via the choledochojejunostomy, are described. The results give insight into the pathophysiological events following major hepatectomy with extrahepatic bile duct resection and choledochojejunostomy. This may help to develop a treatment strategy to reduce postoperative liver failure.

Risk of pancreatic fistula after enucleation of pancreatic tumours
BJS 2015 : 102 : 1258-66

Background: Enucleation is used increasingly for small pancreatic tumours. Data on perioperative outcome after pancreatic enucleation, especially regarding the significance and risk factors associated with postoperative pancreatic fistula (POPF), are limited. This study aimed to assess risk-dependent perioperative outcome after pancreatic enucleation, with a focus on POPF.

Methods: Patients undergoing enucleation for pancreatic lesions between October 2001 and February 2014 were identified from a prospective database. A detailed analysis of morbidity was performed. Risk factors for POPF were assessed by univariable and multivariable analyses.

Results: Of 166 enucleations, 94 (56.6 per cent) were performed for cystic and 72 (43.4 per cent) for solid lesions. Morbidity was observed in 91
patients (54.8 per cent). Severe complications occurred in 30 patients (18.1 per cent), and one patient (0.6 per cent) died. Reoperation was necessary in nine patients (5.4 per cent). POPF was the main determinant of outcome and occurred in 68 patients (41.0 per cent): grade A POPF, 34 (20.5 per cent); grade B, ten (6.0 per cent); and grade C, 24 (14.5 per cent). Risk factors independently associated with POPF were: cystic tumour, localization in the pancreatic tail, history of pancreatitis and cardiac co-morbidity. Only cystic morphology was independently associated with clinically relevant POPF (grade B or C), occurring after enucleation in 25 (27 per cent) of 94 patients with cystic tumours versus nine (13 per cent) of 72 patients with solid tumours. Tumour size and distance to the main duct were not associated with risk of POPF.

Conclusion: Enucleation is a safe procedure in appropriately selected patients with a low rate of severe complications. POPF is the main determinant of outcome and is more frequent after the enucleation of cystic lesions.

Pregnancy and perinatal outcomes in women with polycystic ovary syndrome and twin births: a population-based cohort study
Lovvik TS, Wikstrom AK, Neovius M, et al
BJOG : 2015 : 122 : 1295-1302

Objective: To investigate pregnancy and perinatal outcomes in twin births among women with and without polycystic ovary syndrome (PCOS) diagnosis.
Setting: Sweden.
Population: We identified 20 965 women with twin births between 1995 and 2009 of whom 226 had a PCOS diagnosis through linkage between the Swedish Medical Birth Register and the Swedish National Patient Register.
Methods: Calculating risk ratios (RR) with 95% confidence intervals (CI) using a log-binomial regression model and hazard ratios (HR) with 95% CI for preterm birth.
Main outcome measures: Preterm birth, low birthweight, caesarean section, pre-eclampsia, Apgar score <7 at 5 minutes and perinatal mortality.
Results: PCOS diagnosis in twin pregnancy was associated with increased risk of preterm delivery (51% versus 43%, RR 1.18 [95% CI 1.03-1.37]), particularly spontaneous preterm delivery (37% versus 28%; RR 1.30 [95% CI 1.09-1.55]) and very preterm birth (<32 weeks) (14% versus 8%, RR 1.62 [95% CI 1.10-2.37]). Twins of PCOS mothers had more often low birth weight (48% versus 39%, adjusted RR 1.40 [95% CI 1.09-1.80]). This difference disappeared when adjusting for gestational age. No risk difference was found for caesarean section, pre-eclampsia, low 5-minute Apgar score or perinatal mortality.
Conclusions: The risk of preterm delivery in twin pregnancies is increased by having a PCOS diagnosis. This should be considered in risk estimation and antenatal follow-up of twin pregnancies.

Pain reduction after total laparoscopic hysterectomy and laparoscopic supracervical hysterectomy among women with dysmenorrhoea: a randomised controlled trial
Berner E, Quiqstad E, Myrvold AK, et al
BJOG 2015; 122 : 1102-11

Objective: To evaluate the effectiveness of total laparoscopic hysterectomy compared with laparoscopic, supracervical hysterectomy for alleviating dysmenorrhoea.
Design: Randomised blinded controlled trial.
Setting: Norwegian university teaching hospital.
Sample: Sixty-two women with dysmenorrhoea.
Methods: Participants randomised to either total laparoscopic, hysterectomy (n=31) or laparoscopic supracervical hysterectomy (n=31).
Main outcome measures: The primary outcome measure, measured 12 months after intervention, was reduction of cyclic pelvic pain (visual analogue scale, 0-10). Secondary outcome measures included patient satisfaction (visual analogue scale, 0-10) and quality of life (Short Form 36, 0-100).
Results: The groups were comparable at baseline. There was no difference in self-reported dysmenorrhoea at 12 months (mean 0.8 [SD 1.6] versus 0.8 [SD 2.0], P = 0.94). There was no difference in patient satisfaction (mean 9.3 [SD 1.5] versus 9.1 [SD 1.2], P = 0.66) or quality of life (mean 81.6 [SD 17.8] versus 80.2 [SD 18.0], P = 0.69).
Conclusion: Improvement in dysmenorrhoea and quality of life as well as patient satisfaction were comparable in the medium term when comparing total laparoscopic hysterectomy with laparoscopic supracervical hysterectomy.