

## ABSTRACT FROM CURRENT LITERATURE

### **Benzodiazepine use and risk of Alzheimer's disease: case-control study**

*SB Gage, Y Morde, T Ducruet et al*

*BMJ 2014; 349 : g5205*

**Objectives:** To investigate the relation between the risk of Alzheimer's disease and exposure to benzodiazepines started at least five years before, considering both the dose-response relation and prodromes (anxiety, depression, insomnia) possibly linked with treatment.

**Design:** Case-control study.

**Setting:** The Quebec health insurance program database (RAMQ)

**Participants:** 1796 people with a first diagnosis of Alzheimer's disease and followed up for at least six years before were matched with 7184 controls on sex, age group, and duration of follow-up. Both groups were randomly sampled from older people (age >66) living in the community in 2000-09.

**Main outcome measure:** The association between Alzheimer's disease and benzodiazepine use started at least five years before diagnosis was assessed by using multivariable conditional logistic regression. Ever exposure to benzodiazepines was first considered and then categorised according to the cumulative dose expressed as prescribed daily doses (1-90, 91-180, >180) and the drug elimination half life.

**Results:** Benzodiazepine ever use was associated with an increased risk of Alzheimer's disease (adjusted odds ratio 1.51, 95% confidence interval 1.36 to 1.69; further adjustment on anxiety, depression, and insomnia did not markedly alter this result: 1.43, (1.28 to 1.60)). No association was found for a cumulative dose <91 prescribed daily doses. The strength of association increased with exposure density (1.32 (1.01 to 1.74) for 91-180 prescribed daily doses and 1.84 (1.62 to 2.08) for >180 prescribed daily doses) and with the drug half life (1.43 (1.27 to 1.61) for short acting drugs and 1.70 (1.46 to 1.98) for long acting ones)

**Conclusion:** Benzodiazepine use is associated with an increased risk of Alzheimer's disease. The stronger association observed for long term exposures reinforces the suspicion of a possible direct association, even if benzodiazepine use might also be an early marker of a condition associated with an increased risk of dementia. Unwarranted long term use of these drugs should be considered as a public health concern.

### **Use of clarithromycin and roxithromycin and risk of cardiac death: cohort study**

*H Svanstrom, B Pasternak, A Hviid*

*BMJ 2014; 349 : g4930*

**Objective:** To assess the risk of cardiac death associated with the use of clarithromycin and roxithromycin.

**Design:** Cohort study

**Setting:** Denmark, 1997-2011.

**Participants:** Danish adults, 40-74 years of age, who received seven day treatment courses with clarithromycin (n=160), roxithromycin (n=588), and penicillin V (n=4 355 309)

**Main outcome measures:** The main outcome was risk of cardiac death associated with clarithromycin and roxithromycin compared with penicillin V. Subgroup analyses were conducted according to sex, age, risk score, and concomitant use of drugs that inhibit the cytochrome P450 3A enzyme, which metabolises macrolides.

**Results:** A total of 285 cardiac deaths were observed. Compared with use of penicillin V (incidence rate 2.5 per 1000 person years), use of clarithromycin was associated with a significantly increased risk of cardiac death (5.3 per 1000 person years; adjusted rate 1.76, 95% confidence interval 1.08 to 2.85) but use of roxithromycin was not (2.5 per 1000 person years; adjusted rate ratio 1.04, 0.72 to 1.51). The association with clarithromycin was most pronounced among women (adjusted rate ratios 2.83 (1.50 to 5.36) in women and 1.09 (0.51 to 2.35) in men). Compared with penicillin V, the adjusted absolute risk difference was 37 (95% confidence interval 4 to 90) cardiac deaths per 1 million courses with clarithromycin and 2 (-14 to 25) cardiac deaths per 1 million courses with roxithromycin.

**Conclusions:** This large cohort study found a significantly increased risk of cardiac death associated with clarithromycin. No increased risk was seen with roxithromycin. Given the widespread use of clarithromycin, these findings call for confirmation in independent populations.

### **Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality**

*A Patel, MA Laffan, U Waheed et al.*

*BMJ 2014; 349:g4561*

**Objective:** To assess the efficacy and safety of pooled human albumin solutions as part of fluid volume expansion and resuscitation (with or without improvement of baseline hypoalbuminaemia) in critically unwell adults with sepsis of any severity.

**Design:** Systematic review and meta-analysis of randomised clinical trials, with trial sequential analysis, subgroup, and meta-regression analysis.

**Data sources:** PubMed, Central, Web of Science

(includes Medline, Conference Proceedings Citation Index, Data Citation Index, Chinese Science Citation Database, CAB abstracts, Dentent Innovations Index), OvidSP (includes Entmise, Ovid Meeline, HMIG, PsycINFO, Maternity and Infant Care, Transport Database), Cochrane Library, clinicaltrials.gov, controlled-trials.com, online material, relevant conference proceedings, hand searching of reference lists, and contact with authors as necessary.

**Eligibility criteria:** Prospective randomised clinical trials of adults with sepsis of any severity (with or without baseline hypoalbuminaemia) in critical or intensive care who received pooled human albumin solutions as part of fluid volume expansion and resuscitation (with or without improvement of hypoalbuminaemia.) compared with those who received control fluids (crystalloid or colloid), were included if all-cause mortality outcome data were available. No restriction of language, date, publication status, or primary study endpoint was applied

**Data extraction:** Two reviewers independently assessed articles for inclusion, extracted data to assess risk of bias, trial methods, patients, interventions, comparisons, and outcome. The relative risk of all-cause mortality was calculated using a random effects model accounting for clinical heterogeneity.

**Primary outcome measure:** All-cause mortality at final follow-up.

**Results:** Eighteen articles reporting on 16 primary clinical trials that included 4190 adults in critical or intensive care with sepsis, severe sepsis, or septic shock. A median of 70.0 g daily of pooled human albumin was received over a median of 3 days by adults with a median age of 60.8 years as part of fluid volume expansion and resuscitation, with or without correction of hypoalbuminaemia. The relative risk of death was similar between albumin groups (that received a median of 175 g in total) and control fluid groups (relative risk 0.94; 95% confidence interval 0.87 to 1.01;  $P=0.11$ ;  $I^2=0\%$ )- Trial sequential analysis corrected the 95% confidence interval for random error (0.85 to 1.02;  $D2=0\%$ ). Eighty eight per cent of the required information size (meta-analysis sample size) of 4894 patients was achieved, and the cumulative effect size measure (z score) entered the futility area, supporting the notion of no relative benefit of albumin (GRADE quality of evidence was moderate). Evidence of no difference was also found when albumin was compared with crystalloid fluid (relative Risk 0.93; 0.86 to 1.01;  $P=0.07$ ;  $I^2=0\%$ ) in 3878 patients (GRADE quality

of evidence was high; 79.9% of required information size) or colloid fluids in 299 patients (relative risk 1.04; 0.79 to 1.38;  $P=0.76$ ;  $I^2=0\%$ ) (GRADE quality of evidence was very low. 5.8% of required information size). When studies at high risk of bias were excluded in a predefined subgroup analysis, the finding of no modality benefit remained, and the cumulative z score was just outside the boundary of futility. Overall, the meta-analysis was robust to sensitivity, subgroup, meta-regression, and trial sequential analysis.

**Conclusions:** In this analysis, human albumin solutions as part of fluid volume expansion and resuscitation for critically unwell adults with sepsis of any severity (with or without baseline hypoalbuminaemia) were not robustly effective at reducing all-cause mortality. Albumin seems to be safe in this setting, as a signal towards harm was not detected, but this analysis does not support a recommendation for use.

### **Diagnostic and therapeutic challenges of primary autoimmune, haemolytic anaemia in children**

*JM Vagace, R Bajo, G Gervasini, Vagace JM, et al. Arch Dis Child 2014; 99 : 668-673*

**Abstract :** Autoimmune haemolytic anaemias (AIHAs) are extracorporeal haemolytic anaemias produced by antierythrocyte autoantibodies which cause a shortened red blood cell life span. There are several reasons why the diagnosis and treatment of AIHAs in children represent a bigger challenge than in adult patients, including the presence of particular AIHA types, the uncertainty of serological tests and the limited clinical experience. All these facts have added up to a poor understanding and management of some topics in childhood AIHA. We discuss some of these questions for example, the occurrence of AIHA with negative direct antiglobulin (Combs) test; the correct diagnosis and actual incidence of paroxysmal cold haemoglobinuria, the most appropriate second-line therapy of AIHA in childhood or the management of transfusion procedures in these patients. This review takes a practical point of view, providing with some ground rules on how to identify and deal with these pediatric patients.

### **Hypotonic versus Isotonic Fluids in Hospitalized Children: A Systematic Review and Meta-Analysis**

BA Foster, D Tom, V Hill

*J Pediatr 2014; 165 : 163-9*

**Objective:** To determine whether the use of hypotonic vs isotonic maintenance fluids confers

an increased risk of hyponatremia in hospitalized children.

**Study design:** A search of MEDLINE (1946 to January 2013), the Cochrane Central Registry (1991 to December 2012), Cumulative Index for Nursing and Allied Health Literature (1990 to December 2012), and Pediatric Academic Societies (2000-2012) abstracts was conducted using the terms "hypotonic fluids/saline/solutions" and "isotonic fluids/saline/solutions," and citations were reviewed using a predefined protocol. Data on the primary and secondary outcomes were extracted from original articles by 2 authors independently. Meta-analyses of the primary and secondary outcomes were performed when possible.

**Results:** A total of 1634 citations were screened. Ten studies (n = 893) identified as independent randomized controlled trials were included. Five studies examined subjects in the intensive care unit setting, including 4 on regular wards and 1 in a mixed setting. In hospitalized children receiving maintenance intravenous fluids, hyponatremia was seen more often in those receiving hypotonic fluids than in those receiving isotonic fluids, with an overall relative risk of 2.37 (95% CI, 1.72-3.26). Receipt of hypotonic fluids was associated with a relative risk of moderate hyponatremia (<130 mmol/L) of 6.1 (95% CI, 2.2-17.3). A subgroup analysis of hypotonic fluids with half-normal saline found a relative risk of hyponatremia of 2.42 (95% CI, 1.32-4.45).

**Conclusion:** In hospitalized children in intensive care and postoperative settings, the administration of hypotonic maintenance fluids increases the risk of hyponatremia when compared with administration of isotonic fluids. For patients on general wards insufficient data are available based on the reviewed studies, and individual risk factors must be assessed.

### **Diagnosis and treatment of autoimmune pancreatitis types 1 and 2**

*S Ritz, E Bergmann, L Grenacher et al.*

*BJS 2014; 101 : 1257-1265*

**Background:** Autoimmune pancreatitis (AIP) is characterized by diffuse or focal swelling of the pancreas. AIP has been divided into types 1 and 2. The aim of the study was to evaluate and compare the clinicopathological characteristics, therapy and outcome of patients with AIP.

**Methods:** The medical records of patients diagnosed with AIP between January 2003 and

July 2011 were reviewed. Characteristics of patients with AIP types 1 and 2 were compared with those of patients with those of patients with pancreatic ductal adenocarcinoma (PDAC)

**Results:** AIP was classified as type 1 in 40 patients and type 2 in 32 according to the HISORT Histology, Imaging, Serology, Other organ involvement, Response to therapy) criteria. Patients with histologically confirmed AIP type 2 were younger than those with type 1 (P = 0.005). Some 30 of 32 patients with AIP type 2 were found to have a localized tumour-like, pancreatic mass and underwent pancreatectomy, compared with only 16 of 40 with type 1 (P < 0.001). Three of 25 patients with AIP type 2 presented with raised serum levels of IgG4 compared with 21 of 38 with type 1 (P < 0.001). There was no difference in symptoms and involvement of other organs between AIP types 1 and 2. Presentation with weight loss was more common among patients with PDAC than those with AIP, but there was no difference in pain or jaundice between the groups. Raised serum carbohydrate antigen 19-9 levels were more prevalent in patients with PDAC.

**Conclusion:** Patients with AIP type 2 frequently present with abdominal pain and a tumour-like mass. Differentiating AIP from PDAC is difficult, so making the clinical decision regarding operative versus conservative management is challenging.

### **Outcomes after implementation of a multimodal standard care pathway for laparoscopic colorectal surgery**

*DW Larson, JK Lovelt, RR Cima et al.*

*BJS 2014; 101 : 1023-1030*

**Background:** The aim of the study was to assess which aspects of an enhanced recovery programme are associated with better outcomes following laparoscopic colorectal surgery

**Methods:** A database of laparoscopic colorectal procedures performed in 2011 was reviewed. Elements of the enhanced recovery programme and compliance were evaluated for short-term (30-day) outcomes. Individual elements included gabapentin, celecoxib, intrathecal analgesia, diet, postoperative fluids, and paracetamol/ non-steroidal anti-inflammatory drug pain management.

**Results:** Five hundred and forty-one consecutive procedures were included. Compliance, with the enhanced recovery programme elements ranged from 82.4 to 99.3 per cent. Median length of hospital stay was 3 (i.q.r. 2.5) days, with 25.9 per cent of patients discharged within 48h. Patients

without complication had a medium length of stay of 3 (i.q.r. 2.4) days if compliant and 3 (3.5) days if not (P < 0.001). Low oral opiate intake (oral morphine equivalent of less than 30 mg (odds ratio (OR) 1.97, 95 per cent confidence interval 1.29 to 3.03; P = 0.002), full compliance (OR 2.36, 1.42 to 3.90; P < 0.001) and high surgeon volume (more than 100 cases per year) (OR 1.50, 1.19 to 1.89; P < 0.001) were associated with discharge within 48h. Compliance with the elements of oral intake and fluid management in the first 48 h was associated with a reduced rate of complications (8.1 versus 19.6 per cent; P=0.001). Median oral opiate intake was 37.5 (i.q.r. 0.105) mg in 48h, with 26.2 per cent of patients receiving no, opiates

Conclusion: Compliance with an enhanced recovery pathway was associated with less opiate use, fewer and a shorter hospital stay.

#### **Risk factors for miscarriage from prevention perspective: a nationwide follow-up study**

*SF Nilsson, PK Anderson, KS Larsen et al*  
*BJOG 2014; 121 : 1375-1385*

Objective: To identify notifiable risk factors for miscarriage and to estimate the preventable proportion of miscarriage that could be attributed to these.

Design: Nationwide observational follow-up study.  
Setting: Denmark

Population: Ninety-one thousand four hundred and twenty seven pregnancies included in the Danish National Birth Cohort between 1996 and 2002.

Methods: Information on potentially modifiable risk factors before and during pregnancy was collected by means of computer assisted telephone interviews and linkage with Danish registers, ensuring almost complete follow-up of pregnancy outcome. Modifiable risk factors for miscarriage were identified by multiple Cox regression analysis, which provided the background for our estimations of population attributable fractions. In all, 88,373 pregnancies had full information on all covariates and were included in this analysis.

Main outcome measures: Miscarriage before 22 completed weeks of gestation.

Results: The potentially modifiable pre-pregnant risk factors associated with increased miscarriage risk were: age of 30 years or more at conception, underweight, and obesity- During pregnancy the modifiable risk factors were alcohol consumption, lifting of >20 kg daily, and night work. We estimated that 25.2% of the miscarriages might be

prevented by reduction of all these risk factors to low risk levels. Modification of risk factors acting before and during pregnancy could lead to prevention of 14.7 and 12.5% respectively, of the miscarriages. Maternal age at conception and alcohol consumption were the most important risk factors.

Conclusions: Miscarriage risk is increased by multiple potentially modifiable risk factors and a considerable proportion of miscarriages may be preventable.

#### **Management and outcomes of acute appendicitis in pregnancy-population-based study of over 7000 cases**

*N Abbasi, V Patenaude, HA Abenhaim*  
*BJOG 2014; 121: 1509-1514*

Objective: To compare outcomes and management practices among pregnant and non pregnant women with acute appendicitis.

Design: Population-based matched cohort study.

Setting: United States of America.

Sample: A total of 7114 women with appendicitis among 7,037,386 births,

Methods: Logistic regression analyses to calculate the odds ratio (OR) and corresponding 95% confidence intervals (95% CIs) for variables and outcomes of interest.

Main outcome measures: Maternal morbidities associated with appendicitis; management practices for pregnant and age-matched non pregnant women with appendicitis.

Results: There was an overall incidence of 101.1 cases of appendicitis per 100,000 births. Appendicitis was diagnosed in 35 570 non pregnant women during the corresponding time frame. Peritonitis occurred in 20.3% of pregnant women with appendicitis, with an adjusted OR of 1.3 (95% CI 1.1-1.4) when compared with non-pregnant women with appendicitis. In pregnancy, there was an almost two-fold increase in sepsis and septic shock. transfusion, pneumonia, bowel obstruction. postoperative infection and length of stay >3 days. Whereas 5.8% of appendicitis cases among pregnant women were managed conservatively, they were associated with a considerably increased risk of shock peritonitis and venous thromboembolism as compared to surgically managed cases.

Conclusions: Compared with non-pregnant women, pregnant women with acute appendicitis have higher rates of adverse outcomes. Conservative management should be avoided given the serious risk of adverse outcomes in pregnancy.