Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: the SPACE trial

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Background & aims: Transarterial chemoembolization with doxorubicin-eluting beads (DC Bead; DEB-TACE) is effective in patients with Barcelona clinic liver cancer stage B hepatocellular carcinoma (HCC). The multikinase inhibitor sorafenib enhances overall survival (OS) and time-to-tumor progression (TTP) in patients with advanced HCC. This exploratory phase II trial tested the efficacy and safety of DEB-TACE plus sorafenib in patients with intermediate stage HCC.

Methods: Patients with intermediate stage multinodular HCC without macrovascular invasion (MVI) or extrahepatic spread (EHS) were randomized 1 : 1 to DEB-TACE (150 mg doxorubicin) plus sorafenib 400 mg twice daily or placebo. The primary endpoint was TTP by blinded central review. Secondary endpoints included time to MVI/EHS, OS, overall response rate (ORR) using modified response evaluation criteria in solid tumors, disease control rate (DCR), time to unTACEable progression (TTUP), and safety.

Results: Of 307 patients randomized, 154 received sorafenib and 153 received placebo. Median TTP for subjects receiving sorafenib plus DEB-TACE or placebo plus DEB-TACE was similar (169 vs. 166 days, respectively; hazard ratio (HR) 1.621, 95% confidence interval (CI) 0.979 to 2.676, P = 0.072). Median time to MVI/EHS (HR 0.621, P = 0.076) and OS (HR 0.898, P = 0.29) had not been reached. The ORRs for patients in the sorafenib and placebo groups with post-baseline scans were 55.9% and 41.3%, respectively, and the DCRs were 89.2% and 76.1%, respectively. TTUP was lower with sorafenib than with placebo (HR 1.586; 95% confidence interval, 1.200–2.096; median 95 vs. 224 days). No unexpected adverse events related to sorafenib were observed.

Conclusion: Sorafenib plus DEB-TACE was technically feasible, but the combination did not improve TTP in a clinically meaningful manner compared with DEB-TACE alone.

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A low-cost, user-friendly electroencephalographic recording system for the assessment of hepatic encephalopathy

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Electroencephalography (EEG) is useful to objectively diagnose/grade hepatic encephalopathy (HE) across its spectrum of severity. However, it requires expensive equipment, and hepatogastroenterologists are generally unfamiliar with its acquisition/interpretation. Recent technological advances have led to the development of low-cost, user-friendly EEG systems, allowing EEG acquisition also in settings with limited neurophysiological experience. The aim of this study was to assess the relationship between EEG parameters obtained from a standard-EEG system and from a commercial, low-cost wireless headset (light-EEG) in patients with cirrhosis and varying degrees of HE. Seventy-two patients (58 males, 61±9 years) underwent clinical evaluation, the Psychometric Hepatic Encephalopathy Score (PHES), and EEG recording with both systems. Automated EEG parameters were calculated on two derivations. Strong correlations were observed between automated parameters obtained from the two EEG systems. Bland and Altman analysis indicated that the two systems provided comparable automated parameters, and agreement between classifications (normal vs. abnormal EEG) based on standard-EEG and light-EEG was good (0.6 < k < 0.8). Automated parameters such as the mean dominant frequency obtained from the light-EEG correlated significantly with the Model for End-Stage Liver Disease score (r = −0.39, P < 0.05), fasting venous ammonia levels (r = −0.41, P < 0.01), and PHES (r = −0.49, P < 0.001). Finally, significant differences in light-EEG parameters were observed in patients with varying degrees of HE.

Conclusion: Reliable EEG parameters for HE diagnosing/grading can be obtained from a cheap, commercial, wireless headset; this may lead to more widespread use of this
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An empirical broad spectrum antibiotic therapy in health-care-associated infections improves survival in patients with cirrhosis: a randomized trial

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Early diagnosis and appropriate treatment of infections in cirrhosis are crucial because of their high morbidity and mortality. Multidrug-resistant (MDR) infections are on the increase in health care settings. Health-care-associated (HCA) infections are still frequently treated as community-acquired with a detrimental effect on survival. We aimed to prospectively evaluate in a randomized trial the effectiveness of a broad spectrum antibiotic treatment in patients with cirrhosis with HCA infections. Consecutive patients with cirrhosis hospitalized with HCA infections were enrolled. After culture sampling, patients were promptly randomized to receive a standard or a broad spectrum antibiotic treatment (NCT01820026). The primary endpoint was in-hospital mortality. Efficacy, side effects, and the length of hospitalization were considered. Treatment failure was followed by a change in antibiotic therapy. Ninety-six patients were randomized and 94 were included. The two groups were similar for demographic, clinical, and microbiological characteristics. The prevalence of MDR pathogens was 40% in the standard versus 46% in the broad spectrum group. In-hospital mortality showed a substantial reduction in the broad spectrum versus standard group (6% vs. 25%; \( P = 0.01 \)). In a post-hoc analysis, reduction of mortality was more evident in patients with sepsis. The broad spectrum showed a lower rate of treatment failure than the standard therapy (18% vs. 51%; \( P = 0.001 \)). Length of hospitalization was shorter in the broad spectrum (12.3 ± 7 days) versus standard group (18 ± 15 days; \( P = 0.03 \)). Five patients in each group developed a second infection during hospitalization with a similar prevalence of MDR (50% broad spectrum vs. 60% standard).

Conclusion: A broad spectrum antibiotic therapy as empirical treatment in HCA infections improves survival in cirrhosis. This treatment was significantly effective, safe, and cost saving.

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Hepatitis C reinfection after sustained virological response

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Background & aims: On-going risk behaviour can lead to hepatitis C virus (HCV) reinfection following successful treatment. We aimed to assess the incidence of persistent HCV reinfection in a population of people who inject drugs (PWID) who had achieved sustained virological response (SVR) seven years earlier.

Methods: In 2004–2006 we conducted a multicentre treatment trial comprising HCV genotype 2 or 3 patients in Sweden, Norway and Denmark (NORTH-C). Six months of abstinence from injecting drug use (IDU) was required before treatment. All Norwegian patients who had obtained SVR (\( n = 161 \)) were eligible for participation in this long-term follow-up study assessing virological and behavioural characteristics.

Results: Follow-up data were available in 138 of 161 (86%) individuals. Persistent reinfection was identified in 10 of 94 (11%) individuals with a history of IDU before treatment (incidence rate 1.7/100 person-years (PY); 95% CI 0.8–3.1] and in 10 of 37 (27%) individuals who had relapsed to IDU after treatment (incidence rate 4.9/100 PY; 95% CI 2.3–8.9). Although relapse to IDU perfectly predicted reinfection, no baseline factor was associated with reinfection. Relapse to IDU was associated with age <30 years (vs. ≥40 years) at treatment (adjusted odds ratio [aOR] 7.03; 95% CI 1.78–27.8) and low education level (aOR 3.64; 95% CI 1.44–9.18).

Conclusion: Over time, persistent HCV reinfection was common among individuals who had relapsed to IDU after treatment. Reinfection should be systematically addressed and prevented when providing HCV care for PWID.

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Clinical and immunologic features of ultra-short celiac disease

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Background & aims: The clinical effects of gluten-sensitive enteropathy with villous atrophy limited to the duodenal bulb (D1) have not been delineated in adults with celiac disease. We investigated the sensitivity of D1 biopsy analysis in the detection of celiac disease, the number and sites of biopsies required to detect ultra-short celiac disease (USCD, villous atrophy limited to D1), and the clinical phenotype of USCD.

Methods: We performed a prospective study of 1378 patients (mean age, 50.3 years; 62% female) who underwent endoscopy at a tertiary medical center in the United Kingdom from 2008 through 2014; routine duodenal biopsy specimens were collected from D1 and the second part of the duodenum (D2). Quadrantic D1 biopsy specimens were collected from 171 consecutive patients with a high suspicion of celiac disease (mean age, 46.5 years; 64% female). Clinical data from patients diagnosed with USCD, based on biopsy analysis, were compared with those from patients with conventional celiac disease (CCD) (villous atrophy beyond D1) and individuals without celiac disease (controls). The number of intraepithelial lymphocytes (IELs) and immune phenotypes were
compared between D1 versus D2 in patients with celiac disease.

**Results:** Of the 1378 patients assessed, 268 (19.4%) were diagnosed with celiac disease; 9.7% of these patients had villous atrophy confined to D1 (USCD; \( P < 0.0001 \)). Collection of a single additional biopsy specimen from any D1 site increased the sensitivity of celiac disease detection by 9.3%–10.8% (\( P < 0.0001 \)). Patients with USCD were younger (\( P = 0.03 \)), had lower titers of tissue transglutaminase antibody (\( P = 0.001 \)), and less frequently presented with diarrhea (\( P = 0.001 \)) than patients with CCD. Higher proportions of patients with CCD had ferritin deficiency (\( P = 0.007 \)) or folate deficiency (\( P = 0.003 \)) than patients with USCD or controls. Patients with celiac disease had a median of 50 IELs/100 enterocytes in D1 and a median of 48 IELs/100 enterocytes (\( P = 0.7 \)) in D2. The phenotype of IELs from patients with D1 celiac disease was indistinguishable from those of patients with D2 celiac disease.

**Conclusion:** Collection of a single additional biopsy specimen from any site in the D1 intestine increases the sensitivity of detection for celiac disease. Patients with USCD may have early stage or limited celiac disease, with a mild clinical phenotype and infrequent nutritional deficiencies.

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**Rectal indomethacin does not prevent post-ERCP pancreatitis in consenting patients**

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**Background & aims:** Rectal indomethacin, a nonsteroidal anti-inflammatory drug, is given to prevent pancreatitis in high-risk patients undergoing endoscopic retrograde cholangiopancreatography (ERCP), based on findings from clinical trials. The European Society for Gastrointestinal Endoscopy guidelines recently recommended prophylactic rectal indomethacin for all patients undergoing ERCP, including those at average risk for pancreatitis. We performed a randomized controlled trial to investigate the efficacy of this approach.

**Methods:** We performed a prospective, double-blind, placebo-controlled trial of 449 consecutive patients undergoing ERCP at Dartmouth Hitchcock Medical Center, from March 2013 through December 2014. Approximately 70% of the cohort were at average risk for PEP. Subjects were assigned randomly to groups given either a single 100-mg dose of rectal indomethacin (\( n = 223 \)) or a placebo suppository (\( n = 226 \)) during the procedure. The primary outcome was the development of post-ERC pancreatitis (PEP), defined by new upper-abdominal pain, a lipase level more than 3-fold the upper limit of normal, and hospitalization after ERCP for 2 consecutive nights.

**Results:** There were no differences between the groups in baseline clinical or procedural characteristics. Sixteen patients in the indomethacin group (7.2%) and 11 in the placebo group (4.9%) developed PEP (\( P = 0.33 \)). Complications and the severity of PEP were similar between groups. Per a priori protocol guidelines, the study was stopped owing to futility.

**Conclusion:** In a randomized controlled study of consecutive patients undergoing ERCP, rectal indomethacin did not prevent post-ERCP pancreatitis. ClinicalTrials.gov no: NCT01774604.

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**Long-term results of the European achalasia trial: a multicentre randomised controlled trial comparing pneumatic dilation versus laparoscopic Heller myotomy**

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**Objective:** Achalasia is a chronic motility disorder of the oesophagus for which laparoscopic Heller myotomy (LHM) and endoscopic pneumatic dilation (PD) are the most commonly used treatments. However, prospective data comparing their long-term efficacy is lacking.

**Design:** 201 newly diagnosed patients with achalasia were randomly assigned to PD (\( n = 96 \)) or LHM (\( n = 105 \)). Before randomisation, symptoms were assessed using the Eckardt score, functional test were performed and quality of life was assessed. The primary outcome was therapeutic success (presence of Eckardt score \( \leq 3 \)) at the yearly follow-up assessment. The secondary outcomes included the need for re-treatment, lower oesophageal sphincter pressure, oesophageal emptying and the rate of complications.

**Results:** In the full analysis set, there was no significant difference in success rate between the two treatments with 84% and 82% success after 5 years for LHM and PD, respectively (\( P = 0.92 \), log-rank test). Similar results were obtained in the per-protocol analysis (5-year success rates: 82% for LHM vs. 91% for PD, \( P = 0.08 \), log-rank test). After 5 years, no differences in secondary outcome parameter were observed. Redilation was performed in 24 (25%) of PD patients. Five oesophageal perforations occurred during PD (5%) while 12 mucosal tears (11%) occurred during LHM.

**Conclusion:** After at least 5 years of follow-up, PD and LHM have a comparable success rate with no differences in oesophageal function and emptying. However, 25% of PD patients require redilation during follow-up. Based on these data, we conclude that either treatment can be proposed as initial treatment for achalasia.

Trial registration numbers Netherlands trial register (NTR37) and Current Controlled Trials registry (ISRCTN56304564).

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Proton pump inhibitors affect the gut microbiome

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Background and aims: Proton pump inhibitors (PPIs) are among the top 10 most widely used drugs in the world. PPI use has been associated with an increased risk of enteric infections, most notably Clostridium difficile. The gut microbiome plays an important role in enteric infections, by resisting or promoting colonisation by pathogens. In this study, we investigated the influence of PPI use on the gut microbiome.

Methods: The gut microbiome composition of 1815 individuals, spanning three cohorts, was assessed by tag sequencing of the 16S rRNA gene. The difference in microbiota composition in PPI users versus non-users was analysed separately in each cohort, followed by a meta-analysis.

Results: 211 of the participants were using PPIs at the moment of stool sampling. PPI use is associated with a significant decrease in Shannon’s diversity and with changes in 20% of the bacterial taxa (false discovery rate < 0.05). Multiple oral bacteria were over-represented in the faecal microbiome of PPI-users, including the genus Rothia ($P = 9.8 \times 10^{-38}$). In PPI users we observed a significant increase in bacteria: genera Enterococcus, Streptococcus, Staphylococcus and the potentially pathogenic species Escherichia coli.

Conclusion: The differences between PPI users and non-users observed in this study are consistently associated with changes towards a less healthy gut microbiome. These differences are in line with known changes that predispose to C. difficile infections and can potentially explain the increased risk of enteric infections in PPI users. On a population level, the effects of PPI are more prominent than the effects of antibiotics or other commonly used drugs.

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