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# Quadruple Rescue Therapy after First and Second Line Failure for *Helicobacter pylori* Treatment: Comparison Between Two Tetracycline-Based Regimens

Enzo Ierardi<sup>1</sup>, Antonio Giangaspero<sup>1</sup>, Giuseppe Losurdo<sup>1</sup>, Floriana Giorgio<sup>1</sup>, Annacinzia Amoruso<sup>1</sup>, Vincenzo De Francesco<sup>1,2</sup>, Alfredo Di Leo<sup>1</sup>, Mariabeatrice Principi

1) Section of Gastroenterology, Department of Emergency and Organ Transplantation, University of Bari, Bari

2) Ospedali Riuniti, Gastroenterology Unit, Foggia, Italy

## ABSTRACT

**Background & Aims:** Antibiotic resistance is the main reason for failure of *Helicobacter pylori* (*H. pylori*) treatment. Currently, guidelines recommend a treatment guided by antimicrobial susceptibility testing after two failures. However, microbial culture is not feasible everywhere, and the limited number of effective antibiotics against the bacterium narrows the options; thus a rescue therapy combining antibiotics with a low resistance may be fitting.

**Methods:** Patients who have failed a first-line treatment (either prolonged triple or sequential regimens) and, successively, a levofloxacin-based triple therapy were considered for the study. Subjects underwent urea breath test (UBT), stool antigen test (ST) and endoscopy/histology to confirm the diagnosis. Cytopenia and impaired liver and kidney function were exclusion criteria. Fifty-four subjects were randomized 1:1 to two regimens: RMB Rabeprazole/Rifabutin/Minocycline/Bismuth sub-citrate or MTB Rabeprazole/Tinidazole/Minocycline/Bismuth sub-citrate both for 10 days. The results were checked 6 weeks after the end of therapy with ST/UBT plus endoscopy when indicated.

**Results:** RMB eradicated the bacterium in 21 patients. Two subjects dropped out. The eradication rate was 77.7% (CI 62.0-93.4%) at intention-to-treat and 84.0% (CI 69.6-98.4%) at per-protocol analysis. MTB was successful in 14 patients (51.9%, CI 33.1-70.7%). No patient withdrew from the treatment for adverse events. Drug-related side effects were reported only in 3 subjects, but in all cases the treatment was carried on.

**Conclusions:** The association minocycline/rifabutin seems to have a synergic effect and a good therapeutic outcome in patients who have failed at least two previous regimens, although a trial on a large population is needed.

**Key words:** *Helicobacter pylori* – antibiotic resistance – rescue therapy – rifabutin – minocycline.

# Health-related Quality of Life and Utilities in Gastric Premalignant Conditions and Malignant Lesions: a Multicentre Study in a High Prevalence Country

Miguel Areia<sup>1,2</sup>, Susana Alves<sup>2</sup>, Daniel Brito<sup>2</sup>, Ana Teresa Cadime<sup>2</sup>, Rita Carvalho<sup>2</sup>, Sandra Saraiva<sup>2</sup>, Sara Ferreira<sup>3</sup>, Joana Moleiro<sup>3</sup>, António Dias Pereira<sup>3</sup>, João Carrasquinho<sup>4</sup>, Luís Lopes<sup>4</sup>, José Ramada<sup>4</sup>, Ricardo Marcos-Pinto<sup>1,5,6</sup>, Isabel Pedroto<sup>5,6</sup>, Luís Contente<sup>7</sup>, Liliana Eliseu<sup>7</sup>, Ana Margarida Vieira<sup>7</sup>, Margarida Sampaio<sup>7</sup>, Helena Tavares Sousa<sup>7</sup>, Nuno Almeida<sup>8</sup>, Carlos Gregório<sup>8</sup>, Francisco Portela<sup>8</sup>, Carlos Sofia<sup>8</sup>, Vânia Braga<sup>9</sup>, Elisabete Baginha<sup>10</sup>, Tiago Bana e Costa<sup>10</sup>, Cristina Chagas<sup>10</sup>, Luís Lebre Mendes<sup>10</sup>, Pedro Magalhães-Costa<sup>10</sup>, Leopoldo Matos<sup>10</sup>, Francisco Rocha Gonçalves<sup>1,9</sup>, Mário Dinis-Ribeiro<sup>1,9</sup>

1) Center for Research in Health Technologies and Information Systems, Faculty of Medicine, Porto University; 2) Gastroenterology Dept., Portuguese Oncology Institute of Coimbra; 3) Gastroenterology Dept., Portuguese Oncology Institute of Lisbon; 4) Gastroenterology Dept., Santa Luzia Hospital - Viana do Castelo (Local Health Unit of Alto Minho); 5) Gastroenterology Dept., Santo António General Hospital, Hospital Centre of Porto; 6) Institute of Biomedical Sciences Abel Salazar, University of Porto; 7) Gastroenterology Dept., Hospital Unit of Portimão (Hospital Center of Western Algarve); 8) Gastroenterology Dept., Coimbra University Hospital Center; 9) Gastroenterology Dept., Portuguese Oncology Institute of Porto; 10) Gastroenterology Dept., West Lisbon Hospital Centre, Lisbon, Portugal

## ABSTRACT

**Background & Aims:** A recent review of economic studies relating to gastric cancer revealed that authors use different tests to estimate utilities in patients with and without gastric cancer. Our aim was to determine the utilities of gastric premalignant conditions and adenocarcinoma with a single standardized health measure instrument.

**Methods:** Cross-sectional nationwide study of patients undergoing upper endoscopy (n=1,434) using the EQ-5D-5L quality of life (QoL) questionnaire.

**Results:** According to EQ-5D-5L, utilities in individuals without gastric lesions were 0.78 (95% confidence interval: 0.76-0.80), with gastric premalignant conditions 0.79 (0.77-0.81), previously treated for gastric cancer 0.77 (0.73-0.81) and with present cancer 0.68 (0.55-0.81). Self-reported QoL according to the visual analogue scale (VAS) for the same groups were 0.67 (0.66-0.69), 0.67 (0.66-0.69), 0.62 (0.59-0.65) and 0.62 (0.54-0.70) respectively. Utilities were consistently lower in women versus men (no lesions 0.71 vs. 0.78; premalignant conditions 0.70 vs. 0.82; treated for cancer 0.72 vs. 0.78 and present cancer 0.66 vs. 0.70).

**Conclusion:** The health-related QoL utilities of patients with premalignant conditions are similar to those without gastric diseases whereas patients with present cancer show decreased utilities. Moreover, women had consistently lower utilities than men. These results confirm that the use of a single standardized instrument such as the EQ-5D-5L for all stages of the gastric carcinogenesis cascade is feasible and that it captures differences between conditions and gender dissimilarities, being relevant information for authors pretending to conduct further cost-utility analysis.

**Key words:** gastrointestinal endoscopy – QoL – gastric cancer – intestinal metaplasia – atrophic gastritis.

**Abbreviations:** LYS: life-years saved; QALY: quality-adjusted life years; VAS: visual analogue scale; CI: confidence interval.

# Acute Colonic Diverticulitis: Diagnostic Evidence, Demographic and Clinical Features in Three Practice Settings

Rajan Iyer<sup>1</sup>, George F. Longstreth<sup>1</sup>, Li-Hao Chu<sup>1</sup>, Wansu Chen<sup>1</sup>, Linnette Yen<sup>2</sup>, Paul Hodgkins<sup>2</sup>, Aniket A. Kawatkar<sup>1</sup>

1) Department of Research and Evaluation Kaiser Permanente Southern California, Pasadena, CA; 2) Global Health Economics and Outcomes Research Shire Development LLC, Wayne, P,AUSA

## ABSTRACT

**Background & Aims:** Diverticulitis is often diagnosed in outpatients, yet little evidence exists on diagnostic evidence and demographic/clinical features in various practice settings. We assessed variation in clinical characteristics and diagnostic evidence in inpatients, outpatients, and emergency department cases and effects of demographic and clinical variables on presentation features.

**Methods:** In a retrospective cohort study of 1749 patients in an integrated health care system, we compared presenting features and computed tomography findings by practice setting and assessed independent effects of demographic and clinical factors on presenting features.

**Results:** Inpatients were older and more often underweight/normal weight and lacked a diverticulitis past history and had more comorbidities than other patients. Outpatients were most often Hispanic/Latino. The classical triad (abdominal pain, fever, leukocytosis) occurred in 78 (38.6%) inpatients, 29 (5.2%) outpatients and 34 (10.7%) emergency department cases. Computed tomography was performed on 196 (94.4%) inpatients, 110 (9.2%) outpatients and 296 (87.6%) emergency department cases and was diagnostic in 153 (78.6%) inpatients, 62 (56.4%) outpatients and 243 (82.1%) emergency department cases. Multiple variables affected presenting features. Notably, female sex had lower odds for the presence of the triad features (odds ratio [95% CI], 0.65 [0.45-0.94],  $P<0.05$ ) and increased odds of vomiting (1.78 [1.26-2.53],  $P<0.01$ ). Patients in age group 56 to 65 and 66 or older had decreased odds of fever (0.67 [0.46-0.98],  $P<0.05$ ) and 0.46 [0.26-0.81],  $P<0.01$ ), respectively, while  $\geq 1$  co-morbidity increased the odds of observing the triad (1.88 [1.26-2.81],  $P<0.01$ ).

**Conclusion:** There was little objective evidence for physician-diagnosed diverticulitis in most outpatients. Demographic and clinical characteristics vary among settings and independently affect presenting features.

**Key words:** diverticulitis – abdominal pain – irritable bowel syndrome – fever – leukocytosis – practice setting.

**Abbreviations:** AD: acute colonic diverticulitis; BMI: body mass index; CT: computed tomography; ED: emergency department; IBS: irritable bowel syndrome; ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification; IP: inpatient; KPSC: Kaiser Permanente Southern California; OP: outpatient.

# The Effect of *Lactobacillus reuteri* Supplementation in Adults with Chronic Functional Constipation: a Randomized, Double-Blind, Placebo-Controlled Trial

Veronica Ojetti, Gianluca Ianiro, Annalisa Tortora, Giovanna D'Angelo, Teresa Antonella Di Rienzo, Stefano Bibbò, Alessio Migneco, Antonio Gasbarrini

Department of Medical Sciences, Division of Gastroenterology Catholic University Rome, Italy

## ABSTRACT

**Background & Aims:** There is a growing interest for the use of probiotics for chronic constipation. A recent randomized controlled trial (RCT) showed a positive effect of *Lactobacillus reuteri* (*L. reuteri*) on bowel movement frequency in infants with chronic constipation. The aim of the present study was to evaluate the effects of *L. reuteri* in adult patients with functional constipation.

**Methods:** A double-blind, placebo RCT was conducted in 40 adults (18M/22F, 35±15 years) affected by functional constipation according to the Rome III criteria. Patients were randomly assigned to receive a supplementation of *L. reuteri* (DSM 17938), or matching placebo for 4 weeks. The increase of bowel movements/week was the primary outcome, while the improvement of stool consistency was the secondary outcome.

**Results:** At week 4, the mean increase in bowel movements/week was 2.6 (SD±1.14, 95% CI:1.6-3.6) in the *L. reuteri* group and 1.0 (SD±1. 95% CI:0.12-1.88) in the placebo group (p=0.046). At the end of the treatment, the mean bowel movements/week was 5.28±1.93 in the *L. reuteri* group and 3.89±1.79 in the placebo group. There was a not significant difference in the stool consistency between the two groups.

**Conclusions:** *L. reuteri* is more effective than the placebo in improving bowel movement frequency in adult patients with functional constipation as previously demonstrated in children, even if it seems to have no effect on stool consistency.

**Key words:** bowel movements – bowel – constipation – evacuation – *L. reuteri* – placebo.

# Clinical Usefulness of HCV Core Antigen Assay for the Management of Patients with Chronic Hepatitis C

Dragos Florea<sup>1,2</sup>, Emil Neaga<sup>1</sup>, Ionelia Nicolae<sup>1</sup>, Daniela Maxim<sup>1</sup>, Madalina Popa<sup>1</sup>, Dan Otelea<sup>1</sup>

1) Prof Dr Matei Bals National Institute for Infectious Diseases; 2) Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

## ABSTRACT

**Aim:** The study aimed to evaluate the clinical utility of the chemiluminescent HCV core Ag test compared to viral load assessment in the management of patients with chronic hepatitis C.

**Methods:** A retrospective study was performed at a tertiary-care infectious diseases hospital on samples collected from anti-HCV positive patients. Seventy-six samples were tested with the Architect HCV core Antigen kit and Cobas AmpliPrep/Cobas Taqman HCV kit. The HCV Ag test accuracy was estimated using data from all the HCV RNA tested samples received between January 2011 and December 2012.

**Results:** The HCV Ag test showed a good correlation between the logarithmic values of HCV RNA and HCV Ag ( $R=0.98$ ), with a 100% specificity and PPV, but with reduced sensitivity for viral loads lower than 1,000 UI/mL. In a model using data from 2,478 HCV RNA tested samples and a cut-off of the Ag assay corresponding to 1,000 UI/mL HCV RNA, the Ag test would have a sensitivity of 82.4%, a NPV of 80.9% and a high specificity and PPV (100%) compared to the viral load. The sensitivity would be higher for baseline evaluation compared to on-treatment samples (98.5 vs. 50%). The highest NPV (98%) would be obtained at 48 and 72 weeks after the initiation of treatment, with a sensitivity of 88.2% and 96.1%, respectively.

**Conclusion:** The Architect HCV core Ag assay might be an alternative for the diagnosis of active HCV infection if molecular tests are not available, and a useful method for the evaluation of sustained virological response in treated patients.

**Key words:** hepatitis C – HCV core antigen – HCV viral load.



# The Metabolic Syndrome Is Not Correlated with the Short-term Risk of Decompensation in Patients with Cirrhosis

**Bogdan Procopet<sup>1,2,3</sup>, Oana Farcau<sup>2</sup>, Marius Balagel<sup>1</sup>, Dana Crisan<sup>1,2</sup>, Horia Stefanescu<sup>2</sup>, Andreea Pop<sup>1,2</sup>, Petra Fischer<sup>2</sup>, Alina Habic<sup>1,2</sup>, Corina Radu<sup>1,2</sup>, Marcel Tantau<sup>1,2</sup>, Mircea Grigorescu<sup>1,2</sup>**

1) Gastroenterology Department, Iuliu Hatieganu University of Medicine and Pharmacy; 2) Gastroenterology Department, Prof. Dr. Octavian Fodor Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania; 3) Hepatic Hemodynamic Laboratory, Liver Unit, IDIBAPS, Hospital Clinic, Barcelona, Spain

## ABSTRACT

**Background & Aims:** Obesity proved to favor clinical decompensation in patients with cirrhosis. Our aim was to investigate if metabolic syndrome (MS) in cirrhotic patients represents a risk factor for decompensation.

**Methods:** 704 cirrhotics, included in a MS prevalence study were considered for evaluation; 121 patients were excluded because they did not complete the follow-up and 303 because they were decompensated at the start of the study. The remaining 280 were followed-up for a median period of 28.1±18 months. Patients were censored at the end of follow-up or at occurrence of a liver related event (LRE). Liver related events were considered the following: decompensation (ascites, variceal bleeding, hepatorenal syndrome, jaundice, encephalopathy), hepatocellular carcinoma, portal vein thrombosis and infections.

**Results:** All MS criteria except the abdominal circumference were significantly different between decompensated and compensated patients. HDL-cholesterol levels were lower in decompensated patients. Among the 280 patients who completed the follow-up, 85 (30%) presented LREs. Ascites was the most frequent event. In the univariate analysis of the MS criteria we found a trend to significance of an inverse correlation between MS and LREs. There was no significant difference between patients with or without MS regarding survival free of LREs, 76.7% and 66.5%, respectively. None of the MS criteria reached the level of significance in discriminating patients with and without LREs.

**Conclusions:** In short term, presence of MS was not a risk factor for LREs. In short term, liver function and lower nutritional status influenced the prognosis. In decompensated patients, the MS defining criteria are not applicable.

**Key words:** liver related events – portal hypertension complications – metabolic syndrome – obesity – prognosis

**Abbreviations:** BMI: body mass index; EV: esophageal varices; HR: hazard ration; HVP: hepatic venous pressure gradient; LRE: liver related event; MS: metabolic syndrome; PHT: portal hypertension; WC: waist circumference.

# Clinical Usefulness of Endoscopic Ultrasound-Guided Fine Needle Aspiration for Gastric Subepithelial Lesions Smaller than 2 cm

Kazuya Akahoshi<sup>1</sup>, Masafumi Oya<sup>2</sup>, Tadashi Koga<sup>3</sup>, Hidenobu Koga<sup>4</sup>, Yasuaki Motomura<sup>1</sup>, Masaru Kubokawa<sup>1</sup>, Jyuya Gibo<sup>1</sup>, Kazuhiko Nakamura<sup>5</sup>

1) Department of Gastroenterology, 2) Department of Pathology, 3) Department of Surgery, 4) Division of Central Laboratory, Aso Iizuka Hospital, Iizuka; 5) Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

## ABSTRACT

**Background & Aims:** There is no evidence of postoperative metastasis of gastric gastrointestinal stromal tumors (GISTs) smaller than 2 cm. The aim of this study was to evaluate the clinical usefulness of endoscopic ultrasound guided fine needle aspiration (EUS-FNA) for gastric subepithelial lesions (SELs) smaller than 2 cm.

**Patients and Methods:** Using a prospectively maintained EUS-FNA database, 90 consecutive EUS-FNAs of gastric hypoechoic solid SELs smaller than 2 cm diagnosed by EUS were evaluated retrospectively. The reference standards for the final diagnosis were surgery (n=44) and/or clinical follow-up (n=46) using esophagogastroduodenoscopy (EGD), CT, and/or ultrasonography (US). Additionally, immunophenotyping of specimens obtained by EUS-FNA and surgical resection specimens were compared.

**Results:** The diagnostic rate of EUS-FNA for gastric hypoechoic solid SELs smaller than 2 cm was 73% (66/90). Histological diagnosis of EUS-FNA showed 47 (52%) malignant SELs (44 GISTs, 1 glomus tumor, 1 SEL like cancer, and 1 malignant lymphoma), 19 (21%) benign SELs (14 leiomyomas, 4 ectopic pancreas, and 1 neurinoma), and 24 (27%) indeterminate SELs. In 44 surgically resected cases, the diagnostic accuracy of EUS-FNA using immunohistochemical analysis was 98% (43/44). There were no complications. Appropriate management was performed in 65 out of 66 SELs (98%) diagnosed by definitive EUS-FNA. After surgery, there was no recurrence of malignant SELs.

**Conclusions:** EUS-FNA is an accurate and safe method in the pre-therapeutic diagnosis of gastric SELs smaller than 2 cm. EUS-FNA for gastric SELs smaller than 2 cm is a promising way to permit early management of patients with gastric SELs including GIST.

**Key words:** EUS-FNA – GIST – SMT – subepithelial lesion – stomach – early diagnosis.

**Abbreviations:** EGD: esophagogastroduodenoscopy; EUS: endoscopic ultrasonography; EUS-FNA: endoscopic ultrasound-guided fine needle aspiration; GIST: gastrointestinal stromal tumor; HPF: high power field; SEL: subepithelial lesion; SMT: submucosal tumor.

# TIMP-1 Expression in Human Colorectal Cancer Is Associated with SMAD3 Gene Expression Levels: A Pilot Study

Calin Ionescu<sup>1,2</sup>, Cornelia Braicu<sup>3</sup>, Roxana Chiorean<sup>4</sup>, Roxana Cojocneanu Petric<sup>3,5</sup>, Emilian Neagoe<sup>6</sup>, Laura Pop<sup>3</sup>, Sergiu Chira<sup>3</sup>, Ioana Berindan-Neagoe<sup>3,7,8</sup>

1) Department of Surgery, Iuliu Hatieganu University of Medicine and Pharmacy; 2) Surgery Clinic 1, County Hospital; 3) Research Center for Functional Genomics, Biomedicine and Translational Medicine, Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca, Romania; 4) Department of Dermatology, University of Freiburg, Freiburg, Germany, 5) Faculty of Biology and Geology, Babeş-Bolyai University; 6) Department of Surgery; 7) Department of Functional Genomics and Experimental Pathology, Prof. Dr. I. Chiricuta Oncology Institute; 8) Department of Immunology, Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca, Romania

## ABSTRACT

**Background & Aims:** The prognosis of colorectal cancer (CRC) varies considerably, and there is a compelling need to identify novel biomarkers with prognostic significance. The aim of the present study was to evaluate the prognostic value of a panel of six genes (*CDH1*, *SMAD3*, *TGFβ1*, *ICAM-1*, *TIMP-1* and *MUC12*) in CRC patients.

**Methods.** We evaluated these genes by qRT-PCR in normal and CRC tumor tissue, and correlated the relative gene expression values with clinical, pathological aspects and other biological factors.

**Results.** RNA expression levels of *CDH1*, *SMAD3*, *TGFβ1*, *ICAM-1*, *TIMP-1* and *MUC12* were measured by qRT-PCR in a set of 39 tumor samples and non-cancer tissue. Statistically significant increases in expression levels were found for *ICAM-1* and *TIMP-1* when comparing tumor samples to the non-tumor group.

**Conclusions.** Among the genes which displayed differential expressions between tumor tissue and adjoining normal tissue, the ones that presented statistically significant correlations were *TIMP-1* and *SMAD3*, possibly with prognostic significance.

**Key words:** colorectal cancer – gene expression – prognostic value

**Abbreviations:** CDH1: E-cadherin; CRC: colorectal cancer; E-cadherin: CDH1; EMT: epithelial-mesenchymal transition; IBD: inflammatory bowel disease; ICAM-1: Intercellular Adhesion Molecule 1; MMPs: matrix metalloproteinases; MUC12: Mucin 12, Cell Surface Associated; OS: overall survival; SMAD3: SMAD Family Member; TGF1: Transforming growth factor beta 1; TIMP-1: tissue inhibitor of metalloproteinase-1.

# A Comparison of Three Chromogranin A Assays in Patients with Neuroendocrine Tumours

Lise Brehm Hoej<sup>1</sup>, Tina Parkner<sup>2</sup>, Cindy Soendersoe Knudsen<sup>2</sup>, Henning Grønbaek<sup>1</sup>

1) Department of Medicine V (Hepatology and Gastroenterology); 2) Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark

## ABSTRACT

**Background & Aims:** Chromogranin A (CgA) is the most important general tumour marker used in the diagnosis and follow-up of patients with neuroendocrine tumours (NET). Chromogranin A assays may have different sensitivities, which is of importance for the clinical diagnosis and handling of NET patients. The aim of this study was to compare the clinical sensitivities of three different CgA assays in NET patients.

**Methods:** We measured CgA level in 42 NET patients (male/female: 23/19, median age: 63 years, range 29-85 years). Twenty-five patients had liver metastases, eight had local disease, and nine were disease free after surgery. We studied an in-house RIA: RH RIA assay (Rigshospitalet, Copenhagen, Denmark); NEOLISA™ (Euro Diagnostica, Malmö, Sweden) and EURIA CgA RIA (Euro Diagnostica, Malmö, Sweden).

**Results:** The RH RIA assay showed a clinical sensitivity of 97%, while the NEOLISA and EURIA assays both showed similar clinical sensitivities of 79%. Patients with liver metastases had significantly higher CgA levels compared to disease free patients by all three assays ( $P<0.001$ ), but only the RH RIA assay was able to discriminate between patients with liver metastases and with regional disease ( $P<0.01$ ).

**Conclusion:** Chromogranin A measurements are significantly assay-dependent and caution should be applied in the interpretation of CgA measurement for assessment of NET status. The in-house RH RIA assay was better at predicting NET status than the NEOLISA and EURIA assays.

**Key words:** chromogranin A – neuroendocrine tumor – assay – enzyme-linked immunosorbent assay – radioimmunoassay.

**List of abbreviations:** CgA: chromogranin A; EURIA: Eurodiagnostica, radioimmunoassay; GFR: glomerular filtration rate; NEOLISA: Eurodiagnostica, enzyme-linked immunosorbent assay; NET: neuroendocrine tumour; PET-CT: positron emission tomography; PPI: proton pump inhibitor; RH RIA: Rigshospitalet, radioimmunoassay ; SPECT-CT: single photon emission computed tomography.

## REVIEW

# Non-invasive Biomarkers in Non-Alcoholic Steatohepatitis-induced Hepatocellular Carcinoma

Mihai Voiculescu<sup>1</sup>, Radu M. Nanau<sup>2</sup>, Manuela G. Neuman<sup>2,3</sup>

1) Division of Nephrology and Internal Medicine, Fundeni Clinical Institute and Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; 2) In Vitro Drug Safety and Biotechnology, 3) Department of Pharmacology and Toxicology, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

## ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is by far the most common form of chronic liver disease worldwide, affecting adults as well as children. Under the term of NAFLD there is a wide spectrum of diseases ranging from simple steatosis to the non-alcoholic steatohepatitis (NASH), which can progress to cirrhosis and hepatocellular carcinoma (HCC). Several mechanisms have been described to influence the progression of the disease from the benign NAFL to the aggressive NASH. The imbalance between pro- and anti-oxidant mechanisms and between pro- and anti-inflammatory cytokines is thought to play a pivotal role in the pathogenesis of NAFLD and disease progression toward NASH and fibrosis. The present review intends to look at some of the mechanistic biomarkers to be employed in establishing an early diagnosis in HCC derived from NASH.

**Key words:** non-alcoholic fatty liver disease – non-alcoholic steatohepatitis – hepatocellular carcinoma – biomarkers – non-invasive.

**Abbreviations:** ANGPT: angiopoietin-2; AFP:  $\alpha$ -fetoprotein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CI: confidence interval; COL: collagen; DCP: des-carboxyprothrombin; GT: gamma glutamyl transpeptidase; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HR: hazard ratio; ITG: integrin; LAM: laminin collagen genes; MMP: matrix metalloproteinase; MS: metabolic syndrome; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; PDGFRA: platelet derived growth factor receptor- $\alpha$

## CASE REPORT

# Primary Hepatic Amyloidosis Presenting as Nodular Masses on the Background of Diffuse Infiltration and Extreme Liver Stiffness on MR Elastography

Sivasubramanian Srinivasan<sup>1</sup>, Yi Qi Tan<sup>1</sup>, Hui Seong Teh<sup>1</sup>, Piao Jarrod Lee<sup>2</sup>, Ree Nee Khoo<sup>1</sup>

1) Department of Diagnostic Radiology, 2) Department of Gastroenterology, Khoo Teck Puat Hospital, Singapore 768828 Republic of Singapore

## ABSTRACT

Amyloidosis is characterized by the deposition of extracellular protein material, amyloid, in various organs. The clinical and imaging features of the disease are often nonspecific and a tissue biopsy is often required. We present the case of a 64-year-old man with biopsy proven amyloidosis of the liver. The patient presented with non-specific clinical symptoms. Routine imaging showed hepatomegaly with heterogeneous enhancement, and several large nodular space occupying lesions, mimicking neoplasm. MR elastography revealed an extremely stiff liver. Amyloidosis presenting as multiple nodular masses on the background of diffuse infiltrative pattern or demonstration of extreme stiffness in hepatic amyloidosis on MR elastography have not been described previously.

**Key words:** amyloidosis – liver – computed tomography – magnetic resonance (MR) imaging – MR elastography.

# Hepatic Cyst Infection Following Aspiration Sclerotherapy: a Case Series

**Titus F.M. Wijnands\***, **Marten A. Lantinga\***, **Joost P.H. Drenth**

Department of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, The Netherlands

## **ABSTRACT**

Mass-related symptoms caused by hepatic cysts are effectively treated by aspiration sclerotherapy (AS). This minimal-invasive intervention is regarded as a safe procedure. Hence, occurrence of complications is low. Transient fever is commonly reported as a side effect. However, documentation on a post-procedural hepatic cyst infection as a complication of AS is limited. We present five cases in which a tentative diagnosis of post-procedural hepatic cyst infection was made. Patients typically presented with abdominal pain and fever, had to be admitted to our hospital, and were treated with long term antibiotics. Ultimately, the cyst infection successfully resolved with ciprofloxacin in all cases.

**Key words:** aspiration sclerotherapy – post-procedural hepatic cyst infection – complication.

# **Malignant Familial Adenomatous Polyposis treated by Laparoscopic Colectomy and Ileal Pouch Anal Anastomosis: a Case Report**

**Florin Zaharie<sup>1,2</sup>, George Ciorogar<sup>1,2</sup>, Roxana Zaharie<sup>2,3</sup>, Marcel Tantau<sup>2,3</sup>, Cornel Iancu<sup>1,3</sup>, Lucian Mocan<sup>1,3</sup>**

1) 3rd Surgical Clinic, Iuliu Hatieganu University of Medicine and Pharmacy; 2) Prof. Dr. Octavian Fodor Regional Institute of Gastroenterology and Hepatology; 3) 3rd Medical Clinic, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

## **ABSTRACT**

The mean age of colorectal cancer in untreated familial adenomatous polyposis (FAP) is 39 years. We present the case of a 21-year-old patient with FAP and colorectal cancer. The patient was detected with significant family history: her mother died at age 45 with colon cancer; two uncles were diagnosed with colon cancer at the age of 40 and 43 and one aunt at the age of 45 with colon cancer and gastric cancer. The treatment was laparoscopic restorative proctocolectomy with total excision of the mesorectum and ileal pouch anal anastomosis completed with endoanal excision of inferior rectal polyps. The histopathological report described a well differentiated rectal adenocarcinoma T1N1aMx developed on a tubulo-villous adenoma located on the rectosigmoid junction, the rest of the polyps with benign histology.

**Key words:** familial adenomatous polyposis – laparoscopic proctocolectomy – malignant polyposis – J pouch.



# Disappearance of an Advanced Adenomatous Colon Polyp after Intratumoural Injection with *Viscum album* (European mistletoe) Extract: a Case Report

Tido von Schoen-Angerer<sup>1,4</sup>, Andreas Goyert<sup>2</sup>, Jan Vagedes<sup>1,5</sup>, Helmut Kiene<sup>3</sup>, Harald Merckens<sup>2</sup>, Gunver S. Kienle<sup>3</sup>

1) ARCIM Institute, and 2) Dept of Internal Medicine, Filderklinik, Filderstadt, Germany; 3) Institute for Applied Epistemology and Medical Methodology, University of Witten/Herdecke, Freiburg, Germany; 4) Dept of Pediatrics, Fribourg Hospital HFR, Fribourg, Switzerland; 5) Dept of Pediatrics, University Hospital, Tübingen Germany

## ABSTRACT

**Background & Aim:** Extracts of *Viscum album* (European mistletoe) have immune-stimulatory and cytotoxic effects, with trials showing a well-established effect on the quality of life and prolonged survival in patients with advanced pancreatic cancer. Regression of tumours following intratumoural injection with *Viscum album* extract has been documented in individual cases. However, its influence on colon polyps has not been investigated.

**Case presentation:** We present the case of a 78-year-old Caucasian male who had undergone hemi-colectomy for a stage IIIC colon cancer but who refused adjuvant chemotherapy. Five years later a newly detected high-grade dysplasia colon adenoma was discovered; however, the adenoma could not be resected endoscopically and the patient did not consent to surgery. Intratumoural injections with *Viscum album* L extract (*Quercus*; Iscador®Qu) were administered twice in an attempt to limit tumour growth. Eight months after the second intratumoural injection the adenoma had disappeared and biopsy revealed no intraepithelial dysplasia or adenoma.

**Conclusions:** This is the first report showing complete regression of a colon adenoma after intratumoural injection with *Viscum album* extract. Prospective studies should evaluate if the treatment effect is reproducible and if this approach could be a useful pre-operative measure for colon adenomas too large for endoscopic resection.

**Key words:** colon polyp – colorectal adenoma – *Viscum album* – European mistletoe – tumour regression.