

## GASTROENTEROLOGÍA

### INFLIXIMAB AS RESCUE THERAPY IN ACUTE CORTICOSTEROID RESISTANT ULCERATIVE COLITIS

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**Background.** Efficacy of infliximab (IFX) in ulcerative colitis (UC) has been studied in the ACT1 and ACT2 trials and associated data sources, reporting a reduction of colectomy rate in patients with moderate to-severe UC, but it has been questioned that eligible cases were outpatients judged as low-risk for colectomy. The value of IFX as rescue therapy in severe UC has been scarcely studied and short-and long-term clinical outcomes are controversial. **AIM:** to study the efficacy of infliximab in acute severe UC. **Material and methods.** We are reporting an observational prospective study conducted in two Argentine centers (in Buenos Aires and Mendoza). After infliximab approval in our country, 65 UC patients resistant to 1 week of intravenous steroid were treated with IFX as alternative to colectomy (Male: 29, F: 36, mean age (mea±SEM) n 36.2±2.0, UC duration 5.9±1.5mo, Left-sided: 22, extensive 43). Severity of UC was determined according to "Truelove and Witts" criteria, and also Mayo score was used to evaluate response. **Results.** At baseline time, deep ulcerations were observed in 82% of cases and serum albumin were  $\leq 3$  g/L in 30% of patients; 78% were thiopurine naive and 1/4 of them were within 2 first yrs of the disease. Most patients 45/65 (74%) received complete inductive therapy: mean

number of infusions  $2.95 \pm 0.30$  (range 1 to 15), and 84% started with thiopurines for long term during biologic induction; 2.4% of cases need received continued therapy. After mean follow-up of  $12.3 \pm 1.6$  months 21 patients had required colectomy. Surgery due to primary non-response to infliximab (defined by the lack of clinical response between week 4 and week 12 of therapy after the first IFX infusion) was carried out in 11% of patients. Cumulative probabilities of colectomy at 6, 12, 18 and 24 months were: 13% (n:38) 14% (n:25), 25% (n:19) and 32% (n:14) respectively. Efficacy rates of treatment were 62% at 12 months and 48% at 18 months. Endoscopic evidency of healing at long term follow-up (mean  $14.9 \pm 2.5$  mo) was confirmed in 58% of patient. Of interest, similar efficacy were observed in 73 Crohn's disease patients, of whom 39 (53%) were L2 (colonic location). Adverse event were observed in 17% of patients; acute infusion reactions in 3% of cases. Two patients (one in each center died after colectomy (sepsis: 1, stroke: 1). **Conclusion.** Our results suggest that IFX seems to be an effective rescue therapy in this highly severe group of UC. Early and systematic concurrent use of thiopurines may be the factor that improved clinical short and long term response in this cohort of patients.

### A PROSPECTIVE CASE - CONTROL PILOT STUDY ABOUT THE RELATIONSHIP BETWEEN COLORECTAL POLYPS AND ANGIOTENSIN RECEPTOR BLOCKERS AND ANGIOTENSIN-CONVERTING ENZYME INHIBITOR

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**Introduction.** Angiotensin-receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEI) are widely used drugs. The renin-angiotensin system has been related with angiogenesis and tumor progression. The association of these drugs with colorectal polyps has not described. **Aim.** To determine the risk of colonic polyps in patients under ARBs or ACE inhibitors treatment. **Materials and methods.** A prospective case control study was conducted in a private community hospital in Argentina from August to November 2010. Patients scheduled for an outpatient colonoscopy during this period were included, and were asked to complete a survey with information about their behavioral factors (diet, exercise and smoking), disease history (diabetes, obesity, dislipemia and hypertension), medications (hypolipemiant, antihypertensive and non-steroidal anti-inflammatory drugs) and personal and family history of colorectal neoplasia. In those patients under ARBs or ACEI treatment, type and treatment duration was also consigned. Patients who were under ARBs /ACEI were regarded as "cases" and those without ARBs/ACEI as "controls". We calculated the risk of colorectal polyps, adenomas, advanced neoplastic lesions (ANL) (size > 1

cm, high grade of dysplasia and/or > 75% of villous component) and cancer. Risk was expressed in OR and its 95% confidence intervals (CI). **Results.** 176 patients were analyzed, 48 (27%) cases and 128 (73%) controls. There were no significant differences in patients characteristics between both groups regarding: familiar history of cancer, indication for colonoscopy and tobacco use ( $P > 0.05$ ). There were significant differences between both groups with respect to: average age (64 vs. 56 ( $P < 0.001$ ), diabetes (16% vs. 5% ( $P < 0.03$ )) and BMI (28 vs. 26 ( $P < 0.017$ )) and chronic non steroidal anti-inflammatory drugs (35% vs. 16% ( $P < 0.01$ )). The risk of colonic polyps, adenomas, ANL and colorectal cancer was similar in both groups: OR 1,3 (CI 0.6 – 3.0), OR 1,4 (CI 0.5 – 3.45), OR 1,15 (CI 0.3 – 4.3) OR 5 (CI 0,7 – 43) respectively. We did not find statistical significant differences when analyzing separately those patients taking ACEI and those taking ARBs nor in those under different treatment durations (<5 years, between 5 and 10 years, >10 years). **Conclusion.** In this pilot study we did not find an increased risk of colorectal neoplasia among those patients under ARB or ACEI treatment.

## COMPARISON OF ABDOMINAL BLOATING SEVERITY BETWEEN IRRITABLE BOWEL SYNDROME PATIENTS WITH LOW AND HIGH HYDROGEN PRODUCTION IN LACTULOSE BREATH TEST

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**Introduction.** Irritable bowel syndrome (IBS) is a chronic disorder whose exact etiology remains unknown. There is growing evidence that intestinal microbiota play a role in its development, and that different types of gut flora may determine the frequency of symptoms. Abdominal bloating is a common symptom among IBS patients. We sought to determine the difference in abdominal bloating severity between IBS patients with low (LH2) or high (HH2) breath hydrogen production. **Materials and Methods.** A sequential analysis of lactulose breath tests performed in IBS patients between July 2009 and August 2010 was undertaken. All patients were asked to fill in a validated questionnaire (IBSSS) assessing the severity of their symptoms, including abdominal bloating. Patients were divided in two groups: those with high hydrogen production and those with low hydrogen production in lactulose breath tests. Hydrogen production was measured using the area under the curve of hydrogen concentration /time. For statistical analysis,

chi square test or Fisher's exact test were used to compare categorical variables; comparison of continuous variables was made using the Student's t test or Mann-Whitney U Test for non-parametric variables. A *P* value of less than 0.05 was considered to be significant. **Results.** Two hundred and thirty four patients were included. A statistically significant difference in abdominal bloating severity score was found between LH2 and HH2 groups [7 (5.7-8) vs. 6.5 (5-7.5), *P* = 0,0001]. This difference remained significant also when comparing only constipated patients of both groups [7.5 (6-8.5) vs. 5.8 (3.5-7.2), *P* = 0,0051]. **Conclusion.** Patients with a low hydrogen area under the curve in lactulose breath test, compatible with the predominance of hydrogen-consuming bacteria significantly have more severe abdominal bloating than those IBS patients with an elevated hydrogen pulmonary excretion, irrespective of the predominant clinical cathartic pattern.

## A NOVEL SELECTIVE FORM OF AUTOPHAGY MEDIATED BY VMP1 PLAYS A CRITICAL ROLE IN THE PROTECTIVE CELL RESPONSE TO ACUTE PANCREATITIS

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VMP1 is a transmembrane protein whose expression triggers autophagy and is essential for autophagosome formation in mammalian cells. VMP1 is induced in pancreatic acinar cells upon CCK-receptor hyperstimulation that mimics acute pancreatitis. Our aim was to study the role of VMP1-mediated autophagy in this pathological process. We developed Ela1-VMP1 mice that constitutively express VMP1-EGFP in pancreatic acinar cells. After CCK-Receptor hyperstimulation with cerulein, pancreases were removed. Electron microscopy and immunofluorescence assays of LC3 and trypsinogen showed autophagosomes containing zymogen granules in pancreases from Ela1-VMP1 mice. Magnetic immunoisolation of VMP1-autophagosomes followed by electron microscopy and western blot analysis confirmed VMP1-mediated autophagy of zymogen granules and revealed the participation of the ubiquitin binding protein

p62, which is a cargo recognition protein for autophagy. Using a permeant fluorescent substrate we found that autophagy selectively degrades the pancreatitis-activated zymogen granules since only cerulein-induced activated zymogen granules colocalized with VMP1 and LC3. We named this novel selective autophagy pathway as zymophagy. Downregulation of VMP1 and inhibition of autophagic flow in cell and animal models demonstrated that zymophagy prevents intracellular trypsin activation and cell death. Finally, zymophagy also occurs in human pancreas with pancreatitis. In conclusion, we describe an original selective autophagy pathway mediated by VMP1 that degrades activated zymogen granules, which involves p62 and prevents cell death. Zymophagy is an inducible and selective autophagy pathway that plays a critical role in the protective cell response to disease.

## INCREASED LINE-1 HYPOMETHYLATION IS A UNIQUE FEATURE OF EARLY-ONSET COLORECTAL CANCER

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**Background.** Early-onset CRC (<50 years) accounts for up to 10% of all CRC. In contrast to older cases, early-onset CRC is characterized by more advanced stage, distal location (especially in rectum) and poor prognosis. We have previously shown that the hereditary syndromes, Lynch syndrome and MUTYH-associated CRC, account for only 15-20% of the cases, and the majority do not show microsatellite instability (MSI) and are hence microsatellite stable (MSS). Genome-wide DNA hypomethylation has been recognized as a common epigenetic change in CRCs, which associates with the activation of certain proto-oncogenes and may facilitate chromosomal instability. Hypomethylation of LINE-1 repetitive sequences is a surrogate marker for global DNA hypomethylation, and is also an independent factor for increased cancer-related mortality and overall mortality in CRC patients. However, the methylation status of LINE-1 elements in early-onset CRC compared to older-onset CRC remains unknown. **Patients and methods.** We analyzed a cohort of non-polyposis CRC diagnosed at age <50 recruited in Argentina (Dr. C.B. Udaondo Hospital, n=115) and Spain (Hospital Clinic of Barcelona, Hospital of Donostia; n=70). As a control group, we used a population-based cohort of sporadic CRC aged >50 years recruited in Spain (EPICO-

LON I study), and categorized the tumors by the presence of sporadic MSI (due to somatic promoter hypermethylation of MLH1, n=46) or sporadic MSS (n=89) cancers. In addition, we analyzed a group of Lynch syndrome CRCs recruited at Baylor University Medical Center at Dallas (n=20). The methylation status of LINE-1 repetitive elements in various groups of tumor specimens was analyzed by quantitative bisulfite pyrosequencing. **Results.** The mean LINE-1 methylation levels (+standard deviation, SD) in the four study groups were: early-onset CRC, 56.57% (+8.6); sporadic MSI, 67.14% (+6.2); sporadic MSS, 65.14% (+6.2) and Lynch syndrome, 66.3% (+4.5). Early-onset CRC displayed a significantly lower degree of LINE-1 methylation than any other group (sporadic MSI,  $P < 0.0001$ ; MSS,  $P < 0.0001$ ; Lynch syndrome,  $P < 0.0001$ ). This difference remained significant for both cohorts of early-onset CRC enrolled in Argentina and Spain. **Conclusions.** Our findings demonstrate that a higher degree of LINE-1 hypomethylation is a unique feature of early-onset CRCs, and distinguishes them from older CRCs. Since LINE-1 hypomethylation is a surrogate marker for increased chromosomal instability, our data provide a novel and previously unrecognized explanation for some of the biological differences underpinning early-onset CRCs.

## DIAGNOSTIC YIELD OF UPPER ENDOSCOPY IN TRANSPLANT RECIPIENTS

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**Introduction.** Gastrointestinal symptoms are common among patients who underwent kidney and kidney/pancreas transplantation. Besides the usual causes, patient's symptoms in these cases may be related with immunosuppressive therapy and/or be associated with opportunistic infections (OI). Upper endoscopy is nearly used as a routine tool in the diagnosis work up of disorders with clinical implication. **Aim.** To evaluate the diagnostic yield of upper endoscopy in this population, to describe the endoscopic findings and to assess the clinical endoscopic correlation. **Methods.** Two hundred eighteen computerized clinical records of patients who underwent kidney and kidney/pancreas transplantation were manually reviewed from June 2004 to October 2010 in a third level university hospital. Patients who underwent upper endoscopy due to severe gastrointestinal symptoms (epigastric pain, dysphagia, odynophagia, gastroesophageal reflux symptoms, upper digestive bleeding suspicion) were selected. Demographic, clinical and endoscopic data were reviewed as well as exam results of tissue samples. **Results.** Thirty four (15.6%; 95% CI: 10.5–20.6) of 218 transplant recipients underwent upper endoscopy, mean follow up 26.1 months (1.5–66). Mean age was 45 years (SD 14.5), female/male ratio was 1.2:1. Immunosuppressive therapy with mycophenolate was applied in 30 (88%) of 34 patients. Several frequent symptoms motivated the upper endoscopy: 11 (32%) patients

with epigastric pain, 7 (20.6%) patients with upper digestive bleeding suspicion, 5 (15%) patients with vomits, 4 (12%) patients with odynophagia. Epigastric pain was more frequently observed in OI group (47%) vs. not OI group (27%). Eighty five percent of upper endoscopies were carried out within a 6 months period after transplant procedure. Macroscopic abnormalities were identified in 24 patients (erosions, ulcers, esophagitis, gastropathy). Opportunistic infections were identified in 14 patients (44.2%): 60% cytomegalovirus, 26.7% esophageal candidiasis and 20% invasive strongyloidiasis. The overall mortality rate among transplantation recipients who underwent upper endoscopy was 14.7%. The OI group showed a mortality rate of 21.43% (3 patients) main while the not OI group showed 10% (2 patients). No significant differences was found in the outcome of OI prevalence between kidney transplantation (22) and kidney-pancreas transplantation (12) patients. **Conclusions.** Upper endoscopy followed by adequate sample analysis showed a high diagnostic yield among our patients, mainly due to the identification of significant clinical abnormalities. We conclude that upper endoscopy is a useful procedure to establish OI diagnosis associated with immunosuppression therapy. In addition, we believe that the identification of upper digestive symptoms should raise awareness of the need to carry out this procedure.

## PERSISTENT GALLBLADDER SLUDGE: DEFINITIVE RESULTS OF A LONG TERM FOLLOW UP AFTER SUCCESSFUL ORAL BILE ACID DISSOLUTION

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**Background and Aim.** The gallbladder biliary sludge has been observed in a wide range of clinical disorders (prolonged fast, pregnancy, drugs, enteral nutrition). However, it has been identified as no-innocent, pathological and persistent where the evolution to pancreatitis, cholecystitis or stone progression may be the natural course. The outcome of the pathological gallbladder sludge (GS) after oral bile acid dissolution is unknown. In this prospective experience a population with complete biliary sludge clearance was examined clinically and through ultrasonography (US) during a protocol follow-up to know: gallbladder sludge recurrence (GSR), and development of cholelithiasis. **Materials and methods.** In a prospective study from December 1991 to December 2008 in 221 patients (pts) the diagnosis of GS without stones was made according to the international US criterion. Three months (mo) later a second US control was performed: in 179 pts (81%) the GS disappeared, while in 42 pts (19%) the persistence of the GS was detected. These last were defined as carriers of "persistent gallbladder sludge" (PGS). One hundred percent (42/42) presented biliary pain, 16.6% (7/42) acalculous cholecystitis and 7% (3/42) recurrent acute pancreatitis. Immediately an oral bile acid therapy was started with 12 mg/kg/d of ursodeoxycholic acid (UDCA) for a six-mo period with monthly clinical

examination and US every 2 mo. Between 2 and 6 mo of treatment (mean 3.8 mo) in 100% (42/42) of the pts the GS dissolution was achieved. These 42 were the "study group" and a follow up with clinical and US examination every 6 mo was performed with the administration of only a written low fat diet. The results were evaluated for: GSR and eventual development of cholelithiasis. A minimum follow up of 12 mo was necessary for the evaluation in "results". **Results.** Forty two pts presented PGS (22 female, 25 -72 years, mean 49), in 3 of them the follow-up was lost, then 39 pts without GS were observed for a mean period of 6 years (range 3-17). Seventy four percent of these (29/39) were asymptomatic and presented US normal for 6 years (range 3-17). While the remainder 26% (10/39) presented complications: development of micro-cholelithiasis in 4 cases between 3 and 5 years of evolution (mean 3.5 years), they were treated with laparoscopic cholecystectomy. The other 6 cases developed GSR between 2 and 7 years (mean 5 years) and were successfully retreated with UDCA. **Conclusions.** The 74% of the pts with pathological gallbladder sludge presented a good outcome with a low fat diet, after UDCA therapy. The 26% remainder presented symptomatic biliary complications. News investigations are necessary to confirm this data.

## RISK OF COLORECTAL NEOPLASIA IN PATIENTS WITH CELIAC DISEASE: A MULTICENTRIC STUDY

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**Introduction.** Although lymphoma and small bowel neoplasia are recognized to occur more frequently in patients with celiac disease (CD), an association with colorectal cancer is still controversial. **Aim.** To determine the risk of colorectal neoplasia among patients with celiac disease. **Materials and methods.** A multicentric case-control study was conducted using the Gastroenterology and Endoscopy electronic data base of four community hospitals to identify patients that had performed colonoscopy. Patients with CD were regarded as "cases" and those without CD were regarded as "controls". For each case, two controls matched for age, sex, indication for colonoscopy and first and second grade family history of colorectal cancer, were randomly selected. A survey was carried out by telephone calls to assess patients on their risk factors and history disease. The main outcome evaluated was the risk of colorectal polyps, adenomas, advanced neoplastic lesions (size > 1 cm, villous component > 75% and/or high grade dysplasia) and cancer. Risk was measured in odds ratio (OR) and its corresponding confidence intervals 95% (CI). An univariate analysis was performed to assess characteristics associated with colorectal polyps, adenomas and advanced neoplastic lesions in celiac disease patients and

non celiac patients. **Results.** We identified 118 celiac disease patients who had undergone a previous colonoscopy and were included in the study as cases and 236 as controls. In cases, the average age was 56 (range 22-87), 84% women. The indication for colonoscopy was colorectal cancer screening in 53% and anemia in 15%, with a strict adherence to the gluten-free diet in 65%. Presence of polyps, adenomas and advanced neoplastic lesions was 24/118 (20%), 18/118 (15%) and 3/118 (2.5%), respectively. In controls, the average age was 56 (range 20-87), 84% women, and the indication for colonoscopy was colorectal cancer screening in 51% and anemia in 28%. Presence of polyps, adenomas and advanced neoplastic lesions was 40/236 (17%), 27/236 (11%) and 6/236 (2.5%), respectively. The risk of polyps, adenomas and advanced neoplastic lesions was similar in both groups (OR 1.25, IC 0.71- 2.18,  $P = 0.40$ , OR 1.39, CI 0.73- 2.63,  $P = 0.31$ , and OR 1.00, CI 0.26-3.72,  $P = 1.00$ , respectively). No colorectal cancer was identified. On univariate analysis, no association was found with these lesions in cases and controls. **Conclusion.** In this retrospective cohort study, the risk of colorectal neoplasia among patients with celiac disease was not significantly different from that among non celiac disease controls.



## FUNCTIONAL DYSPESIA AND DUODENAL EOSINOPHILIA: A CASE CONTROL STUDY IN A SOUTH AMERICAN COUNTRY

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**Introduction.** The pathogenesis of functional dyspepsia (FD) is multifactorial, including a possible association between the presence of eosinophils in the duodenal mucosa. The presence of a mild duodenal inflammation could alter sensitivity and duodenal motility in the subgroup of patients with FD- associated postprandial distress. **Aims.** The aim of this observational study was to analyze if an increased number of eosinophils in gastric mucosa (antrum), duodenal bulb (D1) and duodenal second portion (D2) could be associated to dyspepsia postprandial distress symptoms in an adult population. **Methods.** 50 patients were enrolled, following the Rome III criteria, 36 (72%) were female, mean age 52 years, who underwent an upper endoscopy. Biopsy specimens were taken from the antrum, D1 and D2 and were compared with control group (n=50). All of the patients were *H.pylori*-positive. Exclusion criteria: patients with a history of allergy, asthma, parasitic diseases, diabetes, and intake of NSAID. Statistical analysis: proportions and numerical variables were compared in both groups using the X2test and Mann-Whitney test respectively. Odds ratios (OR) were calculated using logistic regression, using, in all cases, a significance level of 0,05.

### Results.

	CASES (n = 50)	CONTROL (n = 50)	P
Average Age	52,58±11	45,38±12	0,003
Sex Female	36 (72%)	30 (60%)	0,20
Eosinophils in the antrum *	26 (15-32)	23 (17-29)	0,0001
Eosinophils bulb *	46 (29-53)	38 (25-46)	<0,0001
Eosinophils in DII *	46,5 (28-54)	38 (28-50)	<0,0001

\* Median (range)

	Cases (n=50)	Control (n=50)	P	OR (CI 95%)
Antral eosinophils > 25	30 (60%)	9 (18%)	<0,0001	6,83 (2,73-17,09)
Eosinophils bulb > 45	28 (56%)	3 (6%)	<0,0001	19,94 (5,47-72,71)
Eosinophils in DII > 45	29 (58%)	4 (8%)	<0,0001	15,88 (4,95-50,96)

**Conclusion.** The average number of eosinophils was significantly higher in the group of patients with FD as compared to control group. This study suggests that duodenal eosinophilia may be associated to FD symptoms. Therefore, diagnostic and therapeutic approaches should be re evaluated in view of this study findings.

## INCREASED PREVALENCE OF CELIAC DISEASE AND POSITIVE MARKERS OF GLUTEN SENSITIVITY IN PATIENTS WITH CHRONIC CONSTIPATION

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**Background.** Although celiac disease (CD) diagnosis is commonly associated with the presence of chronic diarrhea, up to 10% of newly diagnosed cases may present chronic constipation (CC). However, no studies have explored the prevalence of CD or markers of gluten sensitivity among patients consulting by CC. **Aims.** To prospectively determine the prevalence of positive markers of gluten sensitivity and CD in a series of patients with CC. **Methods.** Serum samples from 105 adult consecutive patients (99 females; age range: 18-65 years) attending the Motility and Functional Disorders Unit at a tertiary referral center with a diagnosis of chronic functional constipation (69.5%) or irritable bowel syndrome with constipation (Rome III criteria) were analyzed with a single ELISA assay to detect IgA and IgG antibodies to deamidated gliadin peptides and tissue transglutaminase (DGP/tTG Screen) (cut-off values: >20 U/mL). Seropositive cases were subsequently tested for IgA tissue transglutaminase (IgA tTG), and all DGP/tTG Screen positive patients underwent endoscopic biopsies from the second duodenal portion. The prevalence of CD was compared with that among 518 control subjects referred for routine upper GI endoscopy due to symptoms not primarily related to CD who were tested using the same algorithm.

Diagnosis of CD was based on the presence of a type IIIa Marsh's enteropathy or greater in seropositive cases. **Results.** Ten patients (9.5%) with CC had a positive DGP/tTG Screen test, compared with 45 subjects (8.7%) of the control population. Intestinal biopsy confirmed CD enteropathy in 3 seropositive patients with CC and 13 of the control population. The estimated prevalence was 2.8% for patients with CC and 2.5% for controls. The IgA tTG test was also positive in 5 of the 10 patients with CC, including the 3 cases finally diagnosed with CD, and in 12 control subjects (100% and 92% sensitivity, respectively). Based on positive serology without enteropathy, 7 patients with CC were considered as gluten sensitive. The effect of the gluten-free diet on CC syndrome in CD patients and gluten sensitive patients is still being evaluated. **Conclusions.** This study is the first to discover a high prevalence of CD and gluten sensitivity in patients complaining of CC. This prevalence is almost 3 times greater than that estimated for the Argentinean general population and comparable to that of subjects attending an endoscopic unit. The study shows that the proposed serological assay algorithm was highly sensitive and predictive for diagnosing CD. We recommend screening for CD to patients with CC.

## A DIFFERENTIAL EXPRESSION OF SLAM (SIGNALING AND ACTIVATION OF LYMPHOCYTES MOLECULE) IS INDUCED BY GLIADIN ON ANTIGEN PRESENTING CELLS IN PATIENTS WITH ACTIVE CELIAC DISEASE

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**Background:** Monocytes (Mo) recruited into the intestinal mucosa are source of macrophages and dendritic cells (DC). Under inflammatory conditions, lymphocytes (L) are co recruited and direct (cell to cell contact) or indirectly (by soluble factors) influence Mo outcome. In vitro interactions between blood cells and soluble factors produced by them may influence Mo activation and differentiation into DC. SLAM (Signaling and Activation of Lymphocytes molecule) and OX40 ligand (OX40-L) co-stimulatory molecules expressed on antigen presenting cells (APC) are involved in the interaction with activated L. **Aim.** To examine the influence of gliadin on APC in celiac patients (Ce) and healthy controls (Co) by measuring SLAM and OX40-L expression. **Materials.** 15 adults (> 18y) diagnosed as celiacs and 15 age-matched controls were enrolled. Mo activation: peripheral blood mononuclear cells (PBMC) were isolated, cultured at  $10^6$  cells/ml for 24h with complete RPMI-1640, gliadin (25 ug/ml), urea (2M) and LPS (1 ug/ul), stained with conjugated mAb anti -CD14, -OX40-L and -SLAM, and analyzed by flow cytometry. (FC). Interleukin (IL)-8 was determined by ELISA in supernatants of Mo previously isolated by Percoll gradients. Mo-derive DC: adherent PBMC were incubated with GM-CSF (800U/ml) and IL-4 (10ng/ml) for 5 days, induced to mature in the presence of gliadin (75ug/ml) for 2 days and analyzed for the expression of surfa-

ce CD11c, HLA-DR, CD86, SLAM and OX40-L by FC. Median stimulation indexes ( $\bar{I}$ ) were defined as [gliadin-stimulated Mo or DC / basal Mo or DC] to measure IL-8 production and % of double positive Mo (CD14+ plus SLAM/OX40L) and DC (CD11c+ plus SLAM/OX40-L/ CD86/ HLA-DR). The  $\bar{I}$  were compared by Mann-Whitney test. **Results.** IL-8 was spontaneously released by Mo from Co and Ce ( $P = NS$ ) and further stimulated by gliadin ( $\bar{I}_{IL-8} : 2.70 \pm 0.70$  vs.  $1.40 \pm 0.05$ ,  $P = 0,028$ ; Ce vs. Co). SLAM expression was higher in gliadin-stimulated Mo ( $\bar{I}_{\% CD14+SLAM+} : 10.60 \pm 1.40$  vs.  $6.30 \pm 0.90$ ,  $P = 0,009$ ; Ce vs. Co) and DC ( $\bar{I}_{CD11c+SLAM+} : 6.30 \pm 1.10$  vs.  $3.20 \pm 1.20$ ,  $P = 0,028$ ; Ce vs. Co). After gliadin treatment, similar  $\bar{I}_{\% CD14+CD86}$  and  $\bar{I}_{\% CD14+HLA-DR}$  were calculated in mature DC from Ce and Co ( $P = NS$ ). After gliadin treatments, OX40-L was similarly expressed on Mo and DC from Ce and Co ( $P = NS$ ). **Conclusions.** Although we used both a well-defined cytokine cocktail and gliadin as definite inductors for Mo activation, differentiation and DC maturation, SLAM expression was enhanced on APC from Ce patients. Our results suggest that besides the presence of gliadin, a particular peripheral microenvironment might contribute to the amplification and specialization of the adaptive immune response in celiac disease. The functional involvement of SLAM is currently under investigation.

## ENDOSCOPIA

### COLON CAPSULE ENDOSCOPY IN PEDIATRIC PATIENTS

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The capsule endoscopy (CE) was a technological leap allowing a total exploration of the small intestine (SI) in a simple, ambulatory and minimally invasive manner. The improvements in software and the development of new CE have been constant. New devices as the esophageal capsule for the diagnosis of esophageal varicose veins and for Barrett's esophagus and the colonic for the screening of colon cancer and incomplete colonoscopies represents an important advance. The colonic capsule (CC) has similar dimensions to the one which is used for SI but is has: 2 cameras, automatic control of the luminic exposure, duplicates the speed of register of the images (4/sec) and it has more operative autonomy. These characteristics motivated us to use it in pediatrics, with a modified technique aiming at obtaining better images of the SI and registering images of the whole digestive tract as well. **Material and methods.** Since December, 2009 to August 2010 15 patients were assessed (7♀/8♂), average age 10.8 (range: 6-18). PillCam COLON<sup>®</sup> capsule (Given imaging) 1 hour, 45 minutes previously activated. The indications were: obscure gastrointestinal bleeding (OGIB) in 5 cases, possible inflammatory bowel disease (IBD) in 5 cases, 3 cases of multiple polyposis (2 of Peutz-Jeghers Syndromes, 1 Familial adenomatous polyposis), and 2 patients with colon Crohn's disease (CD). A diet poor in residues and the intake of a polietilenglicol solution was indicated. A capsu-

le was taken spontaneously by 11 children whereas endoscopic assistance was required in 4 patients considering their age or clinic condition. **Results.** In all cases the exploration was total, from mouth to anus. The bidirectional vision managed to capture a larger number of images and facilitated the evaluation of the SI, even when the peristaltic contractions were occurring. By effecting the visualization of the whole digestive tract the presence of lesions which are associated to those of the SI were recorded and the degree of digestive involvement in the cases of polyposis and in one case of one with Blue rubber bleb nevus syndrome was considered.

The cause for the OGIB was evidenced in 4 out of 5 cases: 1 Syndrome of Blue rubber bleb nevus, 1 Graft-versus-host disease and 2 cases of angiodysplasias (1 of the SI and another colonic). In 2 out of 5 patients with a possible Inflammatory Bowel Disease (IBD), images associated to CD were seen in 1 case and in another to a case eosinophilic gastroenteritis. In the 2 patients with confirmed colon CD, the involvement of the SI was excluded. The spontaneous excretion of the capsule occurred at a variable time from 3 to 12 hours; and there was no complication in this group. **Conclusions.** The colon capsule is a safe, efficient and reliable method for pediatric patients and when given after having been previously activated, can display the entire digestive tract.

## RISK OF COLORECTAL POLYPS IN PATIENTS WITH SKIN LESIONS, A PROSPECTIVE CASE-CONTROL PILOT STUDY

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**Introduction.** Skin lesions such as acrochordons (skin tags), seborrheic keratoses, and lentigines have been proposed as markers for adenomatous polyps of the colon, but controversy remains. **Aim.** To assess the risk of colorectal polyps, adenomas and advanced neoplastic lesions (ANL: villous component > 75%, size  $\geq 10$  mm, or high grade dysplasia) in patients with acrochordons, seborrheic keratoses, and lentigines in a private community hospital in Argentina. **Materials and methods.** During February 2010, all patients who underwent a colonoscopy were prospectively assessed by a dermatologist, before the endoscopy procedure, to determine the presence of these skin lesions. Those with previous colonoscopies, incomplete colonoscopies, inadequate intestinal cleansing, or colonic surgeries were excluded. Endoscopists were blind to the dermatologic findings. A case-control study was carried out. Patients with skin lesions were defined as “cases”, and those without them as “controls”. The risk of presenting the mentioned colonic lesions was analyzed, measured in odds ratio (OR) and its corresponding 95% confidence intervals 95% (CI). **Results.** 42

patients were analyzed; the media age was  $59 \pm 12$  years old (range 29-83), 71% were women. Skin tags were found in 23 patients (55%), seborrheic keratoses in 20 patients (48%), and lentigines in 10 patients (24%). Colonic polyps were detected in 21 patients (50%); 14 patients (33%) had adenomas and 7 patients (17%) had ANL. There were no significant differences in the prevalence of adenomatous lesions, neither ANL nor colorectal cancer in those patients with skin tags (OR 1.15 CI 0.33-4.07, OR 1.12 CI 0.24-5.19, OR 2.7 CI 0.34-20, respectively), in those with seborrheic keratoses (OR 0.75 CI 0.21-2.65, OR 3.33 CI 0.64-16.88, OR 3.70, CI 0.47-27.8, respectively), and in those with lentigines (OR 0.16 CI 0.02-1.15, OR 0.48 CI 0.07-3.63,  $p=0.56$ , respectively) comparing with those without them. **Conclusion.** The results of this preliminary study did not show a higher risk of colorectal adenomas or ANL in patients with these lesions. The mere presence of these skin lesions would not be used as an indication for screening colonoscopy.

## CAN HYPERPLASIC-SERRATED LESIONS AND ADENOMATOUS LESIONS BE DIFFERENTIATED DURING A CONVENTIONAL COLONOSCOPY? PREDICTIVE FEATURES BASED ON ENDOSCOPIC CHARACTERISTICS

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**Introduction.** Colonic adenomas are well known as colorectal cancer precursors. Although serrated lesions are currently considered to present an increased risk of cancer, they are macroscopically similar to hyperplastic polyps, and therefore are usually mistaken. **Aims.** To analyze the endoscopic characteristics of the most frequent colonic lesions (hyperplastic, serrated and adenomas) using white-light colonoscopy, and to find out endoscopic predictors of hyperplastic-serrated lesions, which may help to differentiate them from adenomatous lesions. **Material and methods.** We analyzed all resected polyps in every colonoscopy performed in our Unit between May and August 2010. The following characteristics of colonic lesions were analyzed: morphology (sessile or flat vs pedunculated), size ( $<1$ cm vs  $\geq 1$ cm), localization (right vs left colon), presence of mucus covering the lesion, and some combinations of this characteristics. The diagnosis of hyperplastic, serrated and adenomatous lesions was determined histopathologically. Hyperplastic and serrated lesions were analyzed together as a composite endpoint and compared with adenomatous lesions. Endoscopic characteristics significantly related to hyperplastic-serrated lesions were identified by univariate analysis (considering significant an odds ratio (OR) 1 which confidence intervals

(CI) 95% were  $\neq 1$ ). Independent predictors for this group of lesions were also analyzed using a binary logistic regression model. **Results.** We prospectively analyzed 256 colonic lesions. Most of them were sessile (83%) and small (less than 1 cm, 77%); 52% were in the right colon and 12% had mucus on their surface. Histopathologically, 45% were hyperplastic-serrated lesions, and 55% were adenomas. By univariate analysis, we identified the following endoscopic characteristics to be associated with the diagnosis of hyperplastic-serrated lesions: location in the right colon OR 1.77 (CI 1.07-2.93), the presence of mucus OR 6.82 (CI 2.69-17.25), a flat or sessile morphology OR 11.2 (CI 1.44-87), right colon location and having mucus OR 8.88 (CI 2.97-26), the presence of mucus in lesions  $\geq 1$  cm located in the right colon OR 12.3 (CI 1.53-98). By multivariate analyses, the only endoscopic feature independently associated with hyperplastic-serrated histology was the presence of mucus covering the lesion: OR 5.31 (CI 2.04-13.85). **Discussion.** These endoscopic characteristics, which can be easily obtained during a white-light colonoscopy, could be useful to identify hyperplastic-serrated lesions, and to encourage the pathologists to look for serrated features.

## PREVALENCE OF BARRETT'S ESOPHAGUS, DYSPLASIA AND ESOPHAGEAL ADENOCARCINOMA IN A SINGLE CENTRE IN ARGENTINA

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**Background.** Esophageal adenocarcinoma (EAC), the worst complication of gastroesophageal reflux disease (GERD) and Barrett's esophagus (BE), has had an exponential growth in the last four decades. Male gender, white race and age at the time of diagnosis are known risk factors for this disorder. Its correlation with reflux symptoms and whether Intestinal Metaplasia (IM) is a necessary event in the progression of BE to dysplasia and EAC, remain controversial. **Objectives.** To estimate the prevalence of: 1. BE and type of metaplasia, 2. dysplasia and EAC in the BE population, 3. reflux symptoms in these patients. **Materials and Methods.** 21,765 upper endoscopy reports of adults seen at the GI outpatients' clinic in Buenos Aires city between 2001 and 2009 were reviewed. Patients with endoscopic suspicion of BE and columnar metaplasia confirmed on histology were included. Intestinal Metaplasia (IM) was the criterion for the diagnosis of BE. Data collection to assess symptoms was based on the information provided in the "reason for study indication". The study design was descriptive, observational, retrospective, and cross sectional. Statistical analysis: VCCSTAT 2.0 **Results.** 617 patients with endoscopic suspicion of BE were analyzed; 63% were male, average age was 49.5 years (range 14 - 85) and all were white. Columnar metaplasia was confirmed in 586 (95%). Hiatal hernia and esophagitis were described in 44 and 38% of cases respectively. Other endoscopic findings are described in table 1. Histologic findings included: IM in 46% (283/617), glandular metaplasia (GM) in 49%(303/617), and chronic esophagitis in 5% (31/617) of cases. Prevalence of IM in the selected population was

1.3% (CI 95% 1.2-1.5). Prevalence of low grade dysplasia was 3.8% (CI 95% 1.7-7), that of high-grade dysplasia was 2.5 (CI 95% 0.9-5.4) and that of EAC was 2.1% (CI 95% 0.7-4.8) in the BE population; none of these findings were reported in the GM group (Table 1). The prevalence of reflux symptoms (Table 2) was 41% (95% CI 35-47). However, complications of GERD (42%) were the main indication for the procedure (Table 2). **Conclusions.** Prevalence of BE, Low and High Grade Dysplasia in our setting is in keeping with data reported in the literature. Dysplasia or EAC were only observed in the IM group. In view of these findings and that complications prompted endoscopy in most cases, implementation of preventive strategies-emphasizing the importance of a strict protocol for biopsy collection is imperative.

**Table 1.** Endoscopic findings.

Barrett's Esophagus	n	%
Union	271	44,0
< 3 cm (short)	238	38,5
> 3 cm (long)	108	17,5
Total	617	

**Table 2.** Reasons for study indication. Indications for Upper endoscopy.

Symptoms	n	%
Acidity	22	7,8
Heartburn	74	26,1
Epigastralgia	21	7,4
Regurgitation	1	0,4
Control of esophagitis	18	6,4
Surveillance in BE	95	33,6
Control of antireflux surgery	3	1,1
Others	49	17,2
Total	283	100

## ENDOSCOPIC MUCOSAL RESECTION OF 394 CASES OF SESSILE AND FLAT COLORECTAL POLYPS

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**Background.** Adenomatous polyps are predictors of cancer and advanced adenomas. Certain characteristics alert endoscopists about features suggestive of malignancy. Early colorectal cancer (CRC) limited to the superficial submucosa, is considered a low-risk disease for lymphatic and blood dissemination. In these cases, endoscopic mucosal resection (EMR) can be considered a therapeutic option. **Aims.** 1) to describe a large series of colonic polyps resected by EMR, 2) to estimate the prevalence of high grade dysplasia (HGD) and early carcinoma in this cohort. **Materials and methods.** Reports from EMR of colonic polyps were reviewed. Colonoscopies were performed at an outpatient' GI clinic, in Buenos Aires city, between 2004 and 2009. EMR consisted on a sub-mucosal saline injection technique, and main outcome measurement was the description of resected lesions. Statistical analysis: VCCSTAT 2.0. **Results:** 394 EMR of 25,000 colonoscopies were performed in this period. 48 % (190/394) were males. Average age was 56 years (min 24 - max 88 years). All patients were white. 1) With regards polyps' description the most prevalent findings were : by morphology: non - polypoid lesions were detected in 70 %(95%

CI 64-75); by location: most lesions were in right colon :43% (95% CI 39-49); by size: most prevalent size was >10 and ≤ 20 mm in 53% [95% CI 46-57]; by histology: tubular adenoma was the most prevalent lesion, diagnosed in 33% ( 95% CI 28- 38). 2) The prevalence of HGD and early carcinoma was 19% (95% CI 15-23). Predominant characteristics of these 68 lesions are described in Table 1. **Conclusion.** According to these results, morphology and location cannot be used to infer histology as benign and malignant lesions are different in these features. HGD and early carcinoma can be detected in fifth of these lesions, so efforts should aim to promote and improve this effective and safe technique.

**Table 1.** Predominant characteristics of lesions with HGD and early adenocarcinoma.

Most prevalent characteristics of lesions	n lesions	% (95% CI)
Morphology: Polypoid	38	57 (44-69)
Location: Rectum	22	32 (21-44)
Size: >10 and ≤ 20 mm	21	33 (22-46)
Histology: HGD	39	57 (44-69)