cell activation in the context of MDR1α deficiency. Thus, UC patients with combined genetic defects in TLR2 (e.g. R753Q) and ABCB1/MDR1 may exhibit a more severe disease phenotype.

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Mast Cell Activation Syndrome- A Newly Recognized Cause of Recurrent Acute Abdominal Pain

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Background: Patients with mastocytosis or IgE-mediated disorders (ie. food allergy, anaphylaxis) have well characterized gastrointestinal symptoms that may include episodes of abdominal pain, bloating and diarrhea. There is a distinct population of patients, however, who do not meet criteria for mastocytosis and present with similar signs and symptoms. We have identified twenty-five patients in an adult gastroenterology clinic and characterized what is now known as Mast Cell Activation Syndrome (MCAS). Methods: We performed an ongoing review of 25 patients seen at Brigham and Women's Hospital with suspected MCAS from 2004-2009. This diagnosis was reached on clinical grounds based on a typical array of signs and symptoms as well as response to anti-mast cell mediator treatment (ie. mast cell membrane stabilizers, anti-histamines). Each patient had to have a history of abdominal pain, diarrhea and/or bloating and at least two objective findings of a mast cell related disorder such as flushing and dermatographism, or positive laboratory studies indicating mast cell mediator release (ie. 24 hour urine histamine and prostaglandin-D2). Response to anti-mast cell mediator medications was assessed by at least two physicians and graded based on the persistence of mast cell related symptoms (complete response- no further symptoms, excellent response- intermittent persistence of one symptom). Results: Results of all 25 patients are presented in the Table below. Conclusions: MCAS is an under-recognized cause of unexplained recurrent abdominal pain in patients who present to a gastroenterology clinic and frequently exhibit the constellation of clinical symptoms noted above. These patients may or may not have objective laboratory evidence of mast cell mediator release. It is important to be able to recognize this syndrome because response to anti-mast cell mediator medications is often dramatic.

MCAS Manifestation	No. (%)	MCAS phenotype	No. (%)
Abdominal Pain	23 (92)	Female	22 (88)
Diarrhea	17 (68)	Mediator (+) **	14 (56)
Additional constellation: flushing, headache, mental fog, and dermatographism	17 (68)	Response to medications:	
		Complete	5 (20)
		Excellent	15 (60)

** There were no significant differences between the patients that had a positive laboratory finding for a mast cell mediator (mediator (+)) and those that did not with regards to symptoms or signs, or response to anti-mast cell mediator medications.

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Low-Dose Acetylsalicylic Acid use and the Risk of Upper Gastrointestinal Bleeding: A Systematic Literature Analysis

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Introduction: Low-dose acetylsalicylic acid (ASA) is recommended for secondary prevention of cardiovascular disease, but its use is linked to an increased risk of upper gastrointestinal bleeding (UGIB). The strength of this association has not been fully characterized, but is of major importance given the widespread use of low-dose ASA. The aim of this study was to carry out a systematic literature analysis to evaluate the association between low-dose ASA and UGIB. **Methods:** PubMed and EMBASE were searched (1989-2009) for randomized controlled trials (RCTs) reporting UGIB in individuals receiving ASA or placebo, and case-control studies of ASA use in patients with UGIB. Studies were excluded if any of the following applied: ASA dose >325 mg/day, ASA dose not reported, no control group, or all participants given concomitant proton pump inhibitor therapy or *Helicobacter pylori* eradication therapy. **Results:** Searches identified 2011 studies, 22 of which were eligible for inclusion. Fifteen case-control studies analyzed low-dose ASA use in patients with UGIB (n=14 360) and controls with no UGIB (n=44 809). All 15 studies found low-dose ASA to be associated with a significant increase in the risk of UGIB. Five case-control studies (cases: n=9118; controls: n=27 499) assessed the dose-response relationship, three of which found that the risk of UGIB increased with higher doses of ASA. However, even the lowest dose of ASA tested (75 mg/day) was associated with an increased risk of UGIB (odds ratio [OR]: 2.3; 95% confidence interval [CI]: 1.2-4.4). The OR increased to 3.9 (95% CI: 2.5-6.3) in those receiving ASA 300 mg/day. Seven RCTs reported UGIB rates in individuals randomized to receive ASA (dose range: 100 mg every other day to 300 mg/day; n=41 176) or placebo (n=41 216). Mean follow-up periods ranged from 35 days to 10 years. Five of the RCTs reported an increase in the rate of UGIB in individuals receiving low-dose ASA compared with those receiving placebo. No dose-response relationship was seen. The average incidence of UGIB during follow-up, weighted by sample size, was 3.2% (95% CI: 1.2-5.2) in the ASA group and 2.5% (95% CI: 0.4-4.5) in the placebo group. UGIB rates were in the range 1-30 per 1000 per year in the ASA group and 0-11 per 1000 per year in the placebo group. The number of extra UGIB cases associated with ASA use was in the range 0.4-30 per 1000 per year. **Conclusions:** All case-control studies and the majority of RCTs show that low-dose ASA use is associated with an increased risk of UGIB. This increase in risk can be as high as 30 extra cases per 1000 per year. Even the lowest dose tested was associated with an increased risk of UGIB.

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The Impact of Elevated INR on Outcomes in GI Hemorrhage

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Background: Patients admitted for GI bleeding often have INR checked as part of triage. INR has traditionally been used as a marker for coagulopathy, and is often used to risk-stratify patients. It is unclear, however, whether higher INR is associated with poorer outcomes in GI bleeding. We measured the impact of elevated INR on outcomes in a detailed retrospective cohort. **Methods:** We studied patients admitted with GI bleeding in a University-based VA medical center from 1996-2007. Prior to data collection, we created an explicit *a priori* conceptual model to delineate variables that predict outcomes in GI bleeding, including: Charlson comorbidity index, age, meds, history of cirrhosis, bleeding type, vital signs, labs, time of day & week, site of care, receipt of PPI or octreotide, endo findings, type and results of hemostasis, and LOS. Our primary analyses measured the unadjusted relationship between admission INR and 5 outcomes: mortality, time to endo, need for endoscopic hemostasis, 30-day rebleeding, & PRBCs. We then performed multivariable regression adjusting for covariates to isolate the independent effect of INR on outcomes. **Results:** There were 633 patients (age=63±13; Charlson=3.1±3; varices=21%). Median INR was 1.2; 43% had early endo, mean LOS was 7.6 days, 8.5% rebled, and 6.5% died. In unadjusted analysis, for every 1 unit increase in INR there was a 25% increase in the odds of mortality (OR=1.25; CI=1.07-1.47), 2h longer LOS (p<0.05), and 54% reduction in receiving endo within 24h (p<0.05). However, compared to patients with lower INR, those with higher INR had a higher Charlson index (p=0.02), lower initial blood pressure (p=0.007), and higher odds of ICU admission (p=0.04). That is, patients with higher INR had more severe illness vs. those with lower INR. INR predicted receipt of FFP (p<0.001), but not PRBCs (p=0.14), need for hemostasis (p=0.19), or rebleeding (p=0.53). In logistic regression INR was not related to mortality (p=0.56), rebleeding (p=0.24), need for hemostasis (p=0.3), or PRBCs (p=0.052), but did predict longer LOS (p<0.001) and time to endo (p=0.004). **Conclusions:** In a comprehensive database adjusting for a range of confounders, we found no relationship between admission INR and patient outcomes, including mortality, transfusions, need for hemostasis, or rebleeding. In contrast, high INR predicted process measures including use of FFP, admission to ICU, and longer LOS. These data suggest that elevated INR is a marker of overall illness and impacts process of care, but does not drive clinical outcomes; this may have implications for the common practice of delaying process of care in the setting of elevated INR.

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Outcomes of Pregnant Women Hospitalized for Non-Variceal Upper Gastrointestinal Bleeding

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There is sparse population-based data on the management and outcomes of pregnant women hospitalized for non-variceal upper gastrointestinal bleeding (NVUGB). Our aims were to assess utilization of endoscopic procedures and health outcomes in this population. Using the Nationwide Inpatient Sample, which represents a 20% sample of acute-care hospitals in the U.S., we identified pregnant women between 1998-2004 who were admitted for NVUGB (n=722) and age-frequency matched non-pregnant women who were also admitted for NVUGB (in a 1:5 ratio, n=3539 patients). We compared rates of upper endoscopy, mortality, and length of stay between these two groups. As expected, the mean age was similar for both groups (25.3 yrs; range, 14 to 49 yrs). Pregnant women were less likely to be privately insured (39% vs. 47%, P<0.0001) but also less likely to be uninsured (8% vs. 14%, P<0.0001). More than 80% of women in both groups were admitted to large, urban hospitals while 23% were admitted on weekends. Comorbidity as measured by the Charlson Index was lower in pregnant women with 90% having no comorbidity compared to 65% in non-pregnant female controls. The proportion of pregnant women who received upper endoscopy during hospitalization was considerably lower than that in non-pregnant controls (15% vs. 28%, P<0.0001). After adjustment for age, race/ethnicity, comorbidity, health insurance payer, weekend admission, and blood transfusion requirement, pregnant women were less likely to under upper endoscopy compared to non-pregnant women (aOR 0.46; 95% CI: 0.37 - 0.58). However, among those who required upper endoscopy, the time between admission and endoscopy was similar in both groups (1.2 vs. 1.1 days, P=0.5). A lower proportion of pregnant women required transfusion during hospitalization compared to non-pregnant women (2% vs. 8%, P<0.0001). There were no in-hospital deaths among pregnant women which was statistically lower than 0.6% mortality in non-pregnant women. Length of stay was modestly lower in pregnant women (3.0 vs. 3.3 days, P=0.04). Spontaneous abortions and miscarriages occurred in <1% of pregnant women. In conclusion, the management of pregnant women admitted for NVUGB. Pregnant women were healthier and were not at any higher risk of adverse health outcomes compared to non-pregnant women. Further prospective studies are warranted to identify pregnant women with NVUGB to identify those who may benefit from endoscopy and those who would benefit from a more conservative approach.

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Low-Dose Acetylsalicylic Acid in Combination With Clopidogrel, Warfarin, Non-Steroidal Anti-Inflammatory Drugs or Steroids: Risk of Upper Gastrointestinal Bleeding

Luis A. Garcia Rodriguez, Kuei-yu Lin, Sonia Hernandez-Diaz, Saga Johansson

Introduction: Low-dose acetylsalicylic acid (ASA) is often prescribed for patients with cardiovascular disease, either as a monotherapy or administered with other potentially gastrotoxic medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), clopidogrel, warfarin or oral steroids. To date no study has evaluated the risk of upper gastrointestinal bleeding (UGIB) associated with combinations of all these drugs in the same population. This study aimed to quantify the risk of UGIB among users of low-dose ASA alone and in combination with these drugs in UK primary care. **Methods:**The Health Improvement Network UK

primary care database was used to identify all individuals aged 40-84 years with a confirmed diagnosis of UGIB in 1997-2007 (N=2049). An age-, sex- and calendar year-matched control group was identified from the same source population (N=20000). Multivariate logistic regression was used to estimate the relative risk (RR) of UGIB associated with use of low-dose ASA monotherapy and with ASA given concomitantly with clopidogrel, warfarin, NSAIDs or oral steroids. High-dose oral steroids were defined as >10 mg/day prednisolone or the equivalent dose for other steroids. **Results:**Use of low-dose ASA (75-300 mg/day) was associated with a significant increase in the risk of UGIB compared with nonuse (RR 1.80; 95% confidence interval [CI] 1.59-2.03). The risk of UGIB was increased further in individuals who were taking low-dose ASA co-administered with clopidogrel (RR 3.71; 95%CI 2.38-5.76), warfarin (RR 3.62; 95%CI 2.09-6.29) or NSAIDs (RR 4.90; 95%CI 3.86-6.21). In patients who used ASA and concomitant oral steroids, the RR of UGIB was much higher in the group taking high-dose oral steroids (RR 7.87; 95%CI 3.73-16.63) than in those taking low/medium-dose oral steroids (RR 1.80; 95%CI 1.03-3.15). **Conclusions:**Use of low-dose ASA is associated with an almost two-fold greater risk of UGIB than nonuse of ASA. This risk is increased further in individuals who are taking low-dose ASA concomitantly with clopidogrel, warfarin, NSAIDs or high-dose oral steroids.

	UGIB cases (n [%])	Controls (n [%])	Adjusted RR (95% CI)
Non-use of low-dose ASA	1319 (64)	15 584 (78)	1.00 (-)
Current use of low-dose ASA	631 (31)	3778 (19)	1.80 (1.59-2.03)
Non-use of low-dose ASA or clopidogrel	1285 (63)	15 401 (77)	1.00 (-)
Current use of low-dose ASA and clopidogrel	32 (2)	101 (0.5)	3.71 (2.38-5.76)
Non-use of low-dose ASA or warfarin	1220 (60)	14 979 (75)	1.00 (-)
Current use of low-dose ASA and warfarin	20 (1)	55 (0.3)	3.62 (2.09-6.29)
Non-use of ASA or NSAIDs	874 (43)	12 519 (63)	1.00 (-)
Current use of ASA and NSAIDs	129 (6)	323 (2)	4.90 (3.86-6.21)
Non-use of ASA or oral steroids	1225 (60)	14 873 (74)	1.00 (-)
Current use of ASA and high-dose steroids	15 (0.7)	18 (0.1)	7.87 (3.73-16.63)
Current use of ASA and low/medium-dose oral steroids	17 (0.8)	88 (0.4)	1.80 (1.03-3.15)

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Effect of Anti-Secretory Medicines and Nitrates on the Risk of Ulcer Bleeding Among Users of Clopidogrel, Low-Dose Acetylsalicylic Acid, Corticosteroids, Non-Steroidal Anti-Inflammatory Drugs, and Oral Anticoagulants

Kuei-yu Lin, Sonia Hernandez-Diaz, Luis A. Garcia Rodriguez

Objectives: To investigate the effect of different prevention strategies against upper gastrointestinal bleeding (UGIB) in the general population as well as among individuals on antithrombotic or anti-inflammatory treatments. **Methods**: A population-based nested case-control study was conducted using The Health Improvement Network Database. We identified 2049 cases of UGIB between 2000 and 2007. A random sample of 20000 controls was frequency matched to the cases on age, sex, and calendar year. The relative risk (RR) of UGIB associated with each of the gastroprotective agents was estimated by comparing current use, defined as use within one month of the index date, with nonuse in the prior year, using multivariate logistic regression. **Results**: Compared with no proton pump inhibitors (PPI) use in the prior year, current use of PPI for more than 30 days was associated with a reduced risk of UGIB in the general population (adjusted RR 0.80; 95% confidence interval 0.66-0.95). The RR estimate was 1.18 (0.92-1.50) for H2-receptor antagonists (H2RA) and 0.93 (0.76-1.15) for nitrates. The corresponding estimates associated with concomitant PPI use was 0.23 (0.05-1.01) among mono-antiplatelet therapy with clopidogrel, 0.58 (0.42-0.80) among mono-antiplatelet therapy with low-dose acetylsalicylic acid (ASA) 0.21 (0.05-0.87), among dual antiplatelet therapy, 0.48 (0.30-0.77) among traditional non-ASA non-steroidal anti-inflammatory drugs, 0.50 (0.19-1.33) among selective cyclo-oxygenase-2 inhibitors, 0.67 (0.33-1.36) among corticosteroids, and 0.48 (0.22-1.04) among warfarin users. See table. Among individuals on antithrombotic or anti-inflammatory treatments, estimates for H2RA and nitrates were more imprecise and tended to be of a smaller magnitude than the ones of PPI. **Conclusion**: PPI showed a reduced risk of UGIB both overall and among subgroups of users of antithrombotic, corticosteroids and non-steroidal anti-inflammatory drugs.

Population	Exposed group: Current use of PPI with duration>30days		Referent group: Nonuse of PPI in the prior year		Adjusted RR (95% CI)
	Case, N(%)	Control, N(%)	Case, N(%)	Control, N(%)	
All subjects	231(11)	1788(9)	1554(76)	17183(86)	0.80(0.68-0.95)
Mono-antiplatelet clopidogrel users	4(13)	52(31)	23(77)	109(64)	0.23(0.05-1.01)
Mono-antiplatelet ASA users	58(10)	510(14)	453(77)	2880(80)	0.58(0.42-0.80)
Dual antiplatelet therapy	6(19)	36(36)	23(72)	61(60)	0.21(0.05-0.87)
tNSAIDs users	29(9)	154(14)	251(80)	905(79)	0.48(0.30-0.77)
Coxibs users	10(16)	37(19)	46(74)	147(74)	0.50(0.19-1.33)
Corticosteroids users	19(22)	119(27)	59(68)	277(64)	0.67(0.33-1.36)
Warfarin users	12(11)	89(14)	90(80)	502(79)	0.48(0.22-1.04)

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Butyrate-Induced Colonic Hypersensitivity is Mediated by Activation of MAP Kinase That Modulates Transient K^+ Current in Rat Dorsal Root Ganglia Neurons

Dabo Xu, Xiaoyin Wu, Gintautas Grabauskas, Chung Owyang

Butyrate is a short chain fatty acid produced by bacterial fermentation of undigested dietary fibers in the colon. Recent studies showed that fecal butyrate levels were increased in IBS patients. This may have pathophysiological significance as rectal instillation of sodium butyrate (NaB) increased visceral sensitivity in rats. The mechanism responsible for this is unknown. K^+ channels play a pivotal role in modulating excitability of the dorsal root ganglia (DRG) and their downregulation increases pain sensation. We hypothesize that rectal instillation of NaB may lead to activation of the PKC-MAP kinase pathway that modulates transient K^+ current in rat DRG neurons. The enhanced excitability of these neurons may be responsible for colonic hypersensitivity reported in this animal group. To test this hypothesis we performed colorectal distension (CRD) studies in rats treated with NaB rectal instillation. DRG neurons exposed to NaB *In Vivo* and vitro were subjected to whole cell patch clamp recordings and Western blot analysis. Rats received NaB enemas (1 M in 2 ml) daily for 3 days which produced no mucosal abnormalities. 3 days after the first enema, visceromotor responses (VMR) to graded CRD were measured by electromyography. VMRs were markedly enhanced in NaB treated rats. VMR to 20, 40 and 60 mmHg CRD increased from 15, 25 and 33 contractions/5 sec in control to 36, 41 and 55 contractions/5 sec in NaB treated rats ($P<0.05$). Western blot analysis of DRG neurons from NaB treated rats showed a 1.9-fold increase in pERK1/2. Intrathecal administration of the MAP kinase inhibitor U0126 (5 μg) not only normalized the VMRs to CRD in NaB treated rats but also reduced the increase in pERK1/2 by 70%. *In Vivo* studies using isolated DRG neurons projecting to the distal colon showed that NaB (1 mM) caused a 7-fold increase in pERK1/2 and a 2-fold increase in pKv4.2 (a K^+ channel subunit that mediates I_A current). Phosphorylation of Kv4.2 at Thr 602 by ERK results in decreased opening of the K^+ channel and depolarization of the neurons. Pretreatment of the cultured DRG neurons with U0126 (10 μM) prevented the increase in pERK1/2 and pKv4.2 stimulated by NaB (1 mM). Whole-cell patch-clamp recordings showed that NaB (1 mM) caused a 40% reduction in I_A current. These changes were largely prevented by superfusion of U0126 (10 μM). In conclusion, we demonstrated that visceral hypersensitivity induced by colonic NaB treatment is mediated by activation of MAP kinase which phosphorylate Kv4.2. This results in a reduction of I_A current and enhanced DRG neuronal excitability. These findings may have therapeutic significance in IBS patients with colonic hypersensitivity.

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A Candidate Gene Association Study of Functional "Psychiatric" Polymorphisms in Irritable Bowel Syndrome (IBS)

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Background: Psychiatric disorders such as depression, anxiety, and somatization are common co-morbidities of IBS and as such, genetic variants linked to these disorders may be associated with IBS. Specific Aims: To determine whether there is an association between select functional single nucleotide polymorphisms (SNPs) on FKBP5, COMT, NPY, BDNF, ANKK1, DRD2, OPRM1, and FAAH were associated with IBS. Methods: 645 cases with IBS and 323 age, gender, race, and region group-matched controls were selected from a biospecimen resource developed from a previous case-control study (DK66271). Thirteen functional SNPs were selected after performing a literature review of PubMed. Genotyping was performed using an Illumina GoldenGate custom panel. Genotype/allele frequencies were generated for each variant, with comparisons between cases and controls performed with logistic regression. Results: Cases and controls were 50 yrs (median, range: 18.0-70.0), 78% female, 98% Caucasian. The distribution of IBS subtypes among cases was: 172 (27%) IBS-D, 68 (11%) IBS-C, 206 (32%) IBS-M, 195 (230%) other. None of the 13 SNPs were associated with IBS-overall or IBS-D. However, the OPRM SNP was associated with IBS-M (OR=1.47, p=0.034), and IBS-D in females (OR=1.61, p=0.025). The COMT SNP was associated with IBS-C (OR=1.81, p=0.046). The BDNF SNP was also associated with IBS in those with a psychiatric history (OR=2.34, p=0.044), but not among individuals without a psychiatric history. Conclusions: Positive associations were observed between two SNPs on the OPRM and BDNF genes and specific IBS subtypes that will bear further study and reproduction. However, the majority of studied functional SNPs linked with depression, anxiety, and stress response were not associated with IBS suggesting that there may be an etiological difference between psychiatric traits and IBS. Supported by NIH DK66271 and DK076707.

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Glutamatergic Activation of Anterior Cingulate Cortex (ACC) Mediates the Affective Component of Visceral Pain: Acquisition Versus Expression

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Visceral pain contains sensory and affective dimensions. The ACC appears to be involved in the mediation of both pain components. Separating the mechanisms that control the neural pathways mediating pain effect and sensation is a challenge. Using conditioned place aversion (CPA) in rats, we examined whether neurons in the ACC are necessary for the "aversiveness" of visceral nociceptor stimulation, which reflects the affective pain component. We showed that colorectal distension (CRD) induced CPA when paired with a distinct environment context. No initial preference for any of the 3 components (color coded) in the place-conditioning apparatus was detected on the pretest days. After 4 days of conditioning phase training where CRD (40 mmHg; 50 min) was paired with 1/3 compartments, each rat was allowed to move freely throughout the 3 compartments for 20 min with no CRD. A CPA score was generated. Bilateral infusions of the excitotoxin ibotenic acid were made into the ACC to produce neuronal cell loss. In sham lesion rats, CRD-induced a high CPA score (250±20 sec) that persisted for 3-5 wks. In contrast ACC lesioned rats spent