Motility Neurogastroenterology

The characteristics of small intestinal bacterial overgrowth using the lactulose breath test in patients with abdominal bloating
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Background The clinical significances of small intestinal bacterial overgrowth (SIBO) in patients with bloating is still conflicting.

Goal To evaluate the prevalence of SIBO in patients with bloating, and to assess the clinical characteristics according to the presence or subtypes of SIBO.

Study The patients with abdominal bloating undergoing the lactulose breath test (LBT) were investigated to evaluate the prevalence and subtypes of SIBO. Rome III positive IBS and bowel symptoms were surveyed according to the presence or subtypes of SIBO.

Results The prevalence of IBS and SIBO in the patients was 24.0% (86/358) and 37.4% (134/358), respectively. The prevalence and subtypes of SIBO were not different between the IBS and non-IBS patients. Among the 134 SIBO positive (+) patients, 79 (59.0%), 31 (23.1%), 24 (17.9%) were in the SIBO (H₂) +, (CH₄) +, (both) + groups, respectively. The bloating score in the SIBO (H₂) + group was significantly higher than that in the SIBO negative (−) group. The SIBO (CH₄) + group was older, and had higher scores of hard stool and strain than those of the SIBO − group. In the fasting SIBO (H₂) + group (n = 32) diagnosed by increased baseline H₂, the scores for bloating and flatus were higher than those for the SIBO (H₂) + or SIBO − groups.

Conclusions SIBO is associated with patients with a predominance of bloating regardless of IBS. The subtypes of SIBO by the gas pattern and fasting H₂ using the LBT may have effects on the characteristic bowel symptoms.

Key words small intestinal bacterial overgrowth, bloating, lactulose breath test

Novel biomarker panel for the irritable bowel syndrome: a diagnostic blood test is promising
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Background The development of a reliable biomarker for irritable bowel syndrome (IBS) remains one of the major aims of research in functional gastrointestinal disorders (FGIDs). The challenge is formidable in the absence a perfect or even near-perfect reference standard. Previous efforts based on genetic makers and immune parameters have showed promise but have not been robust.

Aims To evaluate an extensive panel of gene expression and serology measures against Rome III criteria for IBS.

Methods Of subjects eligible for analysis (N = 294), 204 met criteria for IBS (69 IBS-C, 75 IBS-D and 60 mixed) while 90 were free of any FGID. A total of 34 markers were selected based on pathways implicated in pathophysiology of IBS or whole human genome screening. Diagnostic models were based on unconditional logistic regression and performance assessed through area under the receiver-operator characteristic curve (AUC), sensitivity and specificity. The potential for over-optimistic performance based on this particular sample was assessed through shrinkage estimators.

Results The performance of a panel of gene expression and serology markers was promising, particularly in discriminating IBS-C from IBS-D where sensitivity 0.88 and specificity 0.84 were achieved. This performance appears to derive largely from a small subset of markers that yield AUC 0.75 (95% CI: 0.67–0.84) in discriminating IBS-C from IBS-D. Discrimination of any IBS from health was also promising with AUC 0.81 (95% confidence interval 0.75–0.87).

Conclusions A combination of gene expression and serological markers shows exciting progress towards a diagnostic test for IBS, particularly in discriminating IBS-C from IBS-D.

Prevalence of constipation in community-dwelling older people in Indonesia
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We identified the prevalence rate of constipation in community-dwelling older Indonesians using Rome III criteria and self-reported constipation.

A cross-sectional, population-based survey using a combination of validated questionnaires was administered by structured interview in participants’ homes in Bali, Indonesia. Six hundred participants were randomly selected from a population of 2,916 (age range from 60 to 102 years).

Three hundred and three participants were interviewed (response rate 51%). They were mostly female (62%) between the ages of 60 to 97 years (mean 68 ± 7.4 (SD) years). Only 4% (n = 12) had symptom profiles that met the full Rome III criteria for constipation. In contrast, 16.5% (n = 50) reported themselves as constipated. 3/12 who met the Rome III criteria considered themselves to be constipated. Of those who self-reported as constipated, 42/50 (84%) did not meet even two of the Rome III criteria for constipation. The agreement between self-reported constipation and Rome III criteria for functional constipation was poor (kappa 0.035), 35/50 (70%) of those with self-reported constipation actively managed their perceived problem, compared to 7/12 (58.3%) of Rome III subjects. Management strategies used by participants in both groups (59/303) included the use of laxative (13/59, 22%), consumption of fibre products (9/59, 15%), diet change (37/59, 62.7%), and visits to health care facilities (10/59, 16.9%). 23/303 participants self-medicated with laxative in the absence of symptoms or without considering themselves to be constipated.

This is the first study to investigate the prevalence of constipation in Indonesia or a south Asian country. The prevalence of Rome III defined constipation is low. This may reflect cultural differences in diet and lifestyle in this older population. The rate of self-management for constipation in the absence of symptoms suggests a need for education within Indonesia around constipation and its treatment.
Modifiable risk factors associated with faecal incontinence in older community dwelling women
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Objectives Faecal incontinence (FI) is a common problem among women in aged care that has been associated with anatomic, physiologic and medical conditions. There are very little data on the risk factors associated with FI in older women still living independently in the community. We aimed to determine if there are any potentially modifiable risk factors associated with FI in a large cohort of older Australian women still living in the community.

Methods Participants were 4889 women (aged 82–87 years) who participated in the fifth survey of the Australian Longitudinal Study on Women’s Health. FI was defined as any leakage of liquid and/or solid stool over the past 12 months. Self-reported symptoms of urinary incontinence, asthma, constipation, high blood pressure, osteoarthritis, osteoporosis, Parkinson’s disease, heart problems, eye disease, cancer, diabetes, stroke, anxiety and depression over the past 12 months were assessed. A lifetime history of prolapse repair and hysterectomy were also recorded. Recorded factors assessed included smoking (never, current, past), alcohol intake (nil, low and high risk), fruit and vegetable intake, body mass index and number of live births. Eight domains of quality of life (QOL) from the valid SF-36 were also assessed. Demographic factors included nationality and marital, educational and socioeconomic status.

Results The prevalence of FI was 25.2% (n = 1231). In a multiple regression model that included all variables, we found reporting urinary incontinence (OR = 2.78; 95%CI 2.28–3.39, P = 0.000), constipation (OR = 1.46; 95%CI 1.22–1.73, P = 0.000), not being a past smoker (OR = 0.64; 95%CI 0.43–0.94, P = 0.000), prolapse repair (OR = 1.62; 95%CI 1.03–2.54, P = 0.036), less serves of fruit (OR = 0.81; 95%CI 0.72–0.91, P = 0.0001), and reduced functioning on the SF–36 subscales of general health (OR = 0.86;95%CI 0.82–0.89, P = 0.000) and role emotional (OR = 0.97; 95%CI 0.95–0.99, P = 0.004) were independently associated with reporting FI versus not reporting FI.

Conclusions FI is a common problem among older community dwelling women. Modifiable risk factors associated with FI in these women include smoking and fruit intake.

Does the biopsychosocial model explain functional gastrointestinal disorders (FGIDs) over time? M JONES, L VAN OUDENHOVE, N KOLOSKI, NJ TALLEY
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Objectives The biopsychosocial model posits that early life factors may influence the later development of psychosocial factors and physiological dysfunction increasing susceptibility to FGIDs, but this has never been studied prospectively. We aimed to test an a priori model of a cyclical relationship between affective disorders and gastrointestinal symptoms with input from personality and childhood abuse.

Methods In an 18 month prospective study, 307 individuals from the community (n = 207 Rome I irritable bowel syndrome and/or functional dyspepsia and n = 100 controls) were interviewed at baseline and every 6 months. A diagnosis of anxiety or depressive disorder was made according to psychiatric DSM-IV criteria. Neuroticism and history of childhood abuse were assessed via validated self-report measures. An a priori hypothesized path model with five timepoints (childhood, baseline, 6, 12 and 18 months) was tested using structural equation modeling.

Results 1) The path model identified both childhood sexual and non-sexual abuse as being associated with baseline levels of depression, but not anxiety. Childhood non-sexual abuse was also directly linked to occurrence of abdominal pain at baseline, whereas neuroticism was strongly associated with baseline anxiety and depression. 2) Baseline anxiety (β = 0.24, p = 0.004), depression (β = 0.18, p = 0.03) and abdominal pain (β = 0.33, p < 0.001) were positively associated with abdominal pain at 6 months. 3) Abdominal pain at 6 months was positively associated with both anxiety (β = 0.46, p < 0.001) and depression (β = 0.62, p < 0.001) at 12 months. 4) Depression at 12 months (β = 0.53, p < 0.001), but not anxiety (β = 0.10, p = 0.16) was associated with abdominal pain at 18 months.

Modifiable risk factors associated with faecal incontinence in older community dwelling women
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Objectives Faecal incontinence (FI) is a common disorder; however no therapy is efficacious, however its benefit against proton pump inhibitor (PPI) therapy, is unknown. We therefore examined the efficacy of Iberogast®, PPI & placebo in patients with FD.

In a double-blind, double dummy, randomised study, FD patients (Rome III criteria) received either; esomeprazole (Nexium) ± placebo (20 mg/day), Iberogast® + placebo (20 drops/TID), dual therapy or double placebo (“active treatment”) for 4 weeks. Thereafter, responders received placebo (“placebo treatment”) for 2 weeks. Ongoing responders were reassessed after 2 weeks of “no treatment”. Symptoms & severity (Nepean Dyspepsia Index [NDI-S], Gastrointestinal Symptom Score [GIS] & Leeds Dyspepsia Questionnaire [LDQ]), quality of life (Nepean Dyspepsia Index [NDI-QoL]) & anxiety & depression (Hospital Anxiety & Depression Scale) were assessed. Visceral hypersensitivity was assessed by nutrient challenge test before & after “active treatment”. Blinded data was divided into “non-responder” & “responder” groups & analysed using non-parametric tests.

50 FD patients have completed the study. 14 (28%) were non-responders (NR) to “active treatment”. Of 36 responders (R), 13 relapsed during “placebo treatment” (36% treatment withdrawal relapers) & 15 relapsed on treatment cessation (42% placebo withdrawal relapers); 8 still had sufficient control of symptoms (22% sustained responders) after 2 weeks of “no treatment”. There were no baseline differences between R & NR. After “active” treatment symptoms & severity decreased in responders (NR vs. R; GIS; 11 ± 2 vs. 6 ± 1, P < 0.01; NDI-S: 60 ± 9 vs. 34 ± 5, P < 0.01; LDQ: 12 ± 1 vs. 9 ± 1, P = 0.05) & this was matched by an improved quality of life (NR vs. R; 46 ± 5 vs. 34 ± 5, P < 0.01). Anxiety, depression & volume consumed during the nutrient challenge test were not different after “active treatment”.

Thus far, 72% of FD patients responded symptomatically to “active treatment” & reported an improved quality of life. The treatment- & placebo-withdrawal relapse rates were also high (36% & 42% of responders).

Unblinded analysis will be of interest to determine whether PPI, Iberogast® or combination yields greater benefits than placebo.
Conclusion There is an ongoing cycle of worsening mood and increasing interference of symptoms on life which is initially driven by early life events, supporting a biopsychosocial framework.

Oesophageal clearance assessment during modified barium swallow studies for dysphagia

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The distinction between oropharyngeal or oesophageal aetiologies of non-structural dysphagia often requires separate investigations and multiple attendances at GI facilities. We have recently incorporated radiological screening of oesophageal dysmotility into modified barium swallow (MBS) studies used to assess oropharyngeal dysphagia. The aim of this study was to assess the reliability and reproducibility of such a combined investigation.

Methods Oesophageal clearance was determined with a novel modified barium oesophageal swallowing scale (MBOSS) (see Table)

<table>
<thead>
<tr>
<th>Severity</th>
<th>Degree of dysmotility</th>
<th>Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Nil</td>
<td>All consistencies cleared in a timely fashion</td>
</tr>
<tr>
<td>1</td>
<td>Mild</td>
<td>Slow to empty, but cleared spontaneously</td>
</tr>
<tr>
<td>2</td>
<td>Mild to Moderate</td>
<td>Cleared with further dry swallows</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Cleared completely with fluid chaser</td>
</tr>
<tr>
<td>4</td>
<td>Moderate to Severe</td>
<td>Cleared partially with fluid chaser</td>
</tr>
<tr>
<td>5</td>
<td>Severe</td>
<td>Unable to clear with strategies trialled</td>
</tr>
</tbody>
</table>

Forty-six cases selected randomly from a database of 144 MBS studies were rated independently for oesophageal clearance by 4 expert raters. Three raters were blinded to all clinical details, whilst the fourth served as a reference standard and had access to all clinical data and the final diagnosis. Intra and inter-rater reliability were determined by Cohen’s kappa for each pair of raters and validity by comparing unblinded with blinded ratings.

Results Intra rater reliability values were 0.770 to 0.820. Inter rater reliability varied between 0.617 and 0.821. The Intraclass correlation coefficient was 0.874. The coefficients for blinded vs. unblinded ratings ranged between 0.617 and 0.79.

Conclusions The MBOSS scale was reproducible within and between raters. Combining oesophageal and oropharyngeal fluoroscopic screening may have value in aiding appropriate triage of patients with swallowing dysfunction to more specialised investigations.

Enkephalin nerve fibres are reduced in some children with slow-transit constipation

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Peripheral-opiate nerve fibres reduce colonic motility and produce constipation. The endogenous opiate enkephalin (ENK) is present in enteric nerve fibres including some containing substance P (SP). Slow-transit constipation (STC) is a form of chronic constipation where motility of the proximal colon is reduced. In STC adults, the number of nerve fibres containing SP and ENK are reduced. In STC children, 25% have decreased SP nerve fibres in colonic circular muscle. Aim: To determine if ENK nerve fibres are reduced in paediatric STC.

Methods Seromuscular biopsies from the right transverse colon were obtained from 51 children (aged 4–14 years) with STC and two control patients with familial adenomatous polyposis (FAP), processed for fluorescence immunohistochemistry to detect SP and ENK immunoreactivity in nerves and imaged using confocal microscopy. Biopsies were qualitatively categorised as having ‘low’ or ‘normal’ levels of SP nerve fibres. Then 12 patients (6 normal and 6 low SP) were randomly selected from the cohort and densities of SP/ENK (SP only), ENK+/SP (ENK only) and SP/ENK+ (co-localised) nerve populations were quantified and analysed for co-localisation.

Results In control (FAP) colon, ENK+ nerve fibres were abundant in the circular and longitudinal muscle but absent from the mucosa. The density of SP and ENK nerve fibres was the same in FAP and ‘normal’ SP patients. In circular muscle, the density of ENK nerve fibres was double the density...
of SP nerve fibres. There were nerve fibres containing ENK only, SP only and both ENK+/SP+ with 34% of ENK nerve fibres containing SP and 41% of SP nerve fibres containing ENK. In the ‘low’ SP patients, there was a 50% reduction in the density of SP nerve fibres (p = 0.01) and ENK nerve fibres (p = 0.05) compared to patients with normal level SP. There was a reduction in ENK only (p = 0.03) and SP only nerve fibres (p = 0.007) but not in SP+/ENK+ nerve fibres. Statistical analysis: unpaired, two-tailed T-tests.

Summary The opiate ENK is abundant in nerve fibres in the muscle layers. One third of the ENK nerve fibres contain SP. One quarter of STC children had low levels of SP nerves and there was a reduction in ENK only and SP only nerve fibres in these patients. There was no reduction in SP+/ENK+ nerve fibres between ‘normal’ and ‘low’ level SP patients. Exogenous opiates cause constipation. Reduced ENK in nerve fibres in the muscle in STC children may contribute to delayed colonic transit. Loss of SP and ENK is more common in adults with STC than in STC children.

Loss of interstitial cells of Cajal (ICC) occurs in a small subgroup of children with slow transit constipation
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Slow-transit constipation (STC) is a form of chronic constipation where motility of the proximal colon is reduced. Gut motility is influenced by Intestinal cells of Cajal (ICC), pacemaker cells that generate an electrical slow wave that propagates through the muscle. Adults with STC have reduced numbers of ICC. Aim: To quantify ICC density in paediatric STC and correlate with SP nerve fibre density and colonic transit rate.

Methods Colonic seromuscular biopsies were obtained from right and left transverse colon from 46 STC children (2–14 years) and 2 children with familial adenomatous polyposis (FAP), processed for fluorescence immunohistochemistry to detect ICC (c-kit) and substance P (SP) immunoreactivity, and images of circular muscle were collected using confocal microscopy. Samples were qualitatively categorised as having ‘normal’ or ‘low’ density of ICC and SP using a scale of 0 (non present) to 3 (strong immunofluorescence). There were ICC containing ENK. In the ‘low’ SP patients, there was a 41% of SP nerve fibres and correlate with SP nerve density (p = 0.001). There was a correlation between ICC density and SP nerve fibre density (p = 0.007) with 73% of patients with ‘normal’ ICC (n = 30) and ‘normal’ SP levels, and 80% with ‘low’ ICC (n = 10) had ‘low’ SP and 6 patients inconclusive. Low ICC density also correlated with more severe STC as determined by nuclear transit study images at 6, 24, 30 and 48 hours (p = 0.03).

Summary Adults with STC have low levels of ICC. Only ¼ of STC children had low ICC with ICC density reduced by 65%. Reduced ICC levels correlated with reduced SP nerve fibres and severe slow transit. While the reduction of ICC in the colon is associated with disrupted colonic motility, it is not clear if loss of ICC is primary or secondary. As ¼ of the STC children have normal ICC density, loss of ICC is not essential for slow colonic transit.

Cricopharyngeal dilatation for post laryngectomy dysphagia – a pilot study of efficacy and safety
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Background and Aims Post laryngectomy dysphagia is an under recognised, multifactorial problem resulting in significant morbidity and potentially mortality. Pharyngeal neuromyopathic dysfunction is frequently present, but the contribution to dysphagia from fibrotic stenosis at the pharyngo-oesophageal junction is unclear. No data exists on the efficacy of cricopharyngeal dilatation, nor predictors of outcome in these patients. In this pilot study, our aim was to determine the efficacy and safety of cricopharyngeal dilatation in this population group.

Methods We conducted a retrospective chart review of all laryngectomees presenting to our multidisciplinary Swallow Clinic between Jan 2008–May 2011 who had undergone cricopharyngeal dilatation. Patients were excluded if they had comorbid neurological conditions associated with oropharyngeal dysphagia or coexisting oesophageal structural lesions. Serial step-wise Savary cricopharyngeal dilatations (q2–6 weeks) were performed at the discretion of the reviewing physician/endoscopist until dysphagia had largely resolved or it was felt a maximal safe dilatation had been achieved. Global assessment of dysphagia severity was made using a 4 point scale. “Response” was defined as a good or excellent response. (Patients with no response or those with a minimal improvement &/or only mild upgrade in diet, were considered treatment failures).

Results Nine patients (7 male; age 48–80 yrs) were analysed a median of 6 yrs post laryngectomy (range 1–18 yrs). All had received radiotherapy; one chemo-radiotherapy. A total of 23 dilatations were performed (median 3, range 1–5 per patient). The median change in maximum diameter achieved with progressive dilatation was 3 mm (range 1–4 mm). Median end maximal diameter achieved was 14 mm (range 10–17 mm). Seven patients demonstrated post-dilatation mucosal tears on reinspection. Minor haemorrhage was common but there were no complications. Six of 9 (67%) responded to dilatation (4 excellent; 2 good).

Conclusions Cricopharyngeal dilatation for post-laryngectomy dysphagia appears to be safe with reasonable efficacy. These findings justify a prospective controlled study to determine efficacy and predictors of outcome.

Oesophageal dysmotility in laryngectomy patients – is there an association?
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Background and Aims Post laryngectomy dysphagia is an under recognised problem with significant morbidity. While primarily related to pharyngeal neuromyopathic dysfunction and pharyngo-oesophageal junction fibrotic stenosis, we have encountered several laryngectomees with oesophageal dysphagia and no apparent stenosis and/or little response to cricopharyngeal dilatation. Many have clinical, endoscopic, radiological and manometric findings suggestive of oesophageal dysmotility.

Methods We conducted a retrospective chart review of all laryngectomees presenting to our multidisciplinary Swallow Clinic with dysphagia between Jan 2008–May 2011. All underwent gastroscopy and cricopharyngeal dilatation in an attempt to treat any mechanical component. If no
obvious stenosis was identified, no mucosal tear was noted on dilatation, or clinical and endoscopic features suggested oesophageal dysmotility, manometry and radiographic swallow studies were organised.

**Results** Nine patients were analysed a median of 6 years post laryngectomy (range 1–18 years). Of this cohort, 4 patients (3 male) aged 62–80 years old, 6–16 years post laryngectomy had features suggestive of oesophageal dysmotility. All received radiotherapy; one chemo-radiotherapy. Three had prominent liquid dysphagia and regurgitation with variable onset (usually several years postlaryngectomy and radiotherapy); they underwent progressive Savary dilatation of the cricopharyngeus segment or any anastomotic stricture with minimal if any benefit. Radiographic swallow studies in these individuals demonstrated a dilated oesophagus with features suggestive of aperistalsis. On oesophageal manometry, all 4 patients had marked aperistalsis, of whom 2 had classic achalasia demonstrating an associated hypertensive lower oesophageal sphincter with failure of relaxation.

**Conclusions** In this small case series, we report a hitherto unrecognised association between laryngectomy ± radiotherapy and significant oesophageal dysmotility – either achalasia or complete aperistalsis. Significant co-existent oesophageal dysmotility needs to be considered in the dysphagic laryngectomee, particularly if they fail to respond to dilatation of the frequently identified concurrent cricopharyngeal stricture. While the mechanism is unknown, we postulate it may be related to enteric neuropathy secondary to surgery ± radiotherapy affecting oesophageal peristalsis.

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**Modulation of distension-induced upper oesophageal sphincter reflexes by 5-HT₃ receptor blockade**

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**Background** A high density of 5-HT₃ receptors are found in the dorsal medulla on vagal afferent terminations implying that 5-HT₃ mediates vagal reflexes at a central level. Although the specific role of 5-HT₃ containing nerves or receptors on oesophageal afferents is not clear, it is thought to modulate intrinsic sensory pathways.

**Aim** To examine the effect of 5-HT₃ blockade on the distension-induced Upper Oesophageal Sphincter (UOS) reflexes.

**Methods** In 18 healthy volunteers a manometry catheter was positioned in the oesophagus with a 6 cm sleeve device straddling the UOS. A centre core exiting 10 cm distal to the mid UOS was used for rapid oesophageal air insufflations (5 repeats of 5, 10, 20 & 30 mls). Subsequently, one group (n = 9) received Ondansetron (8 mg i.v.) and the second group (n = 9) received NaCl (0.9% w/v) and rapid air insufflations were repeated. Frequencies of UOS contractile and relaxation responses were scored before and after treatment with Ondansetron or NaCl.

**Results** 5-HT₃ blockade with Ondansetron had no significant effect of either UOS contractile or relaxation responses.

**Conclusion** Neither distension-induced UOS relaxation reflex nor UOS contractile reflex, is attenuated by 5-HT₃ receptor blockade.