Neurogastroenterology & Motility

Neurogastroenterol Motil (2011) **23,** 8–23 doi: 10.1111/j.1365-2982.2010.01612.x

REVIEW ARTICLE

Evaluation of gastrointestinal transit in clinical practice: position paper of the American and European Neurogastroenterology and Motility Societies

S. S. C. RAO,* M. CAMILLERI,† W. L. HASLER,‡ A. H. MAURER,§ H. P. PARKMAN,¶ R. SAAD,‡ M. S. SCOTT,** M. SIMREN,†† E. SOFFER‡‡ & L. SZARKA†

*Division of Gastroenterology/Hepatology, University of Iowa Carver College of Medicine, Iowa City, IA, USA
†CENTER Program, Mayo Clinic, Rochester, MN, USA
‡Department of Gastroenterology, University of Michigan, Ann Arbor, MI, USA
§Department of Radiology, Temple University School of Medicine, Philadelphia, PA, USA
¶ Division of Gastroenterology Section, Department of Medicine, Temple University School of Medicine, Philadelphia, PA, USA
**Academic Surgical Unit and Neurogastroenterology Group, Barts and The London School of Medicine and Dentistry, London, UK
††Department of Gastroenterology, University of Gothenburg, Sweden
‡‡Department of Gastroenterology, Cedars Sinai Medical Center, Los Angeles, CA, USA

Abstract

Background *Disorders of gastrointestinal (GI) transit and motility are common, and cause either delayed or accelerated transit through the stomach, small intestine or colon, and affect one or more regions. Assessment of regional and/or whole gut transit times can provide direct measurements and diagnostic information to explain the cause of symptoms, and plan therapy.* ***Purpose*** *Recently, several newer diagnostic tools have become available. The American and European Neurogastroenterology and Motility Societies undertook this review to provide guidelines on the indications and optimal methods for the use of transit measurements in clinical practice. This was based on evidence of validation including performance characteristics, clinical significance, and strengths of various techniques. The tests include measurements of: gastric emptying with scintigraphy, wireless motility capsule, and ^{13}C breath tests; small bowel transit with breath tests, scintigraphy, and wireless motility capsule; and colonic transit with radioopaque markers, wireless motility capsule, and scintigraphy. Based on the evidence, consensus recommendations are provided for each technique and for the evaluations of regional and whole gut transit. In summary, tests of gastrointestinal transit are available and useful in the evaluation of patients with symptoms suggestive of gastrointestinal dysmotility, since they can provide objective diagnosis and a rational approach to patient management.*

Keywords *breath tests, dysmotility, gastrointestinal transit, radioopaque markers, scintigraphy, wireless motility capsule.*

Address for Correspondence
Satish S. C. Rao, 4612 JCP, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA 52242-1009, USA.
Tel: 319 353 6602; fax: 319 353 6399;
e-mail: satish-rao@uiowa.edu
Received: 1 July 2010
Accepted for publication: 8 September 2010

INTRODUCTION

Gastroparesis, constipation, irritable bowel syndrome, and functional dyspepsia affect over one-third of the population, consume significant health care resources, affect quality of life, and cause distress. They are associated with alterations in gastrointestinal (GI) transit of food, chyme, and residue. Assessment of regional (e.g., gastric, small intestinal, or colonic

transit) or whole gut transit time can facilitate diagnosis and rational management of these disorders.

Advances in techniques together with the availability of several new tests for the evaluation of GI transit, and a lack of information, led The American Neurogastroenterology and Motility Society and the European Society of Neurogastroenterology and Motility to establish a task force to examine the diagnostic utility of these techniques and make recommendations for their use in clinical practice. The task force performed appropriate literature search using PubMed, Google scholar and Medline and held numerous discussions and conference calls to develop this narrative review and provide consensus guidelines that appraise the transit tests under three main regions; stomach, small bowel, and colon. Scintigraphy and wireless motility capsule assess both regional and whole gut transit and are discussed in multiple sections.

ASSESSMENT OF GASTRIC EMPTYING

The stomach accommodates and temporarily stores food, triturates and mixes it with secretions, and empties food (chyme) in an orderly fashion into the small intestine. Gastric emptying tests are used to evaluate patients with upper GI symptoms; they detect delayed (gastroparesis) or rapid emptying (dumping syndrome). Several tests are available to assess gastric emptying and the pros and cons of some common techniques are discussed in Table 1. For this test and others discussed in this manuscript, we have used a semi-quantitative score that was developed by us for the purposes of this document because there is no validated scale. This scoring system has not been validated but we hope will serve as a template for comparison of the various tests.

Table 1 Pros and cons of tests for the assessment of gastric emptying

Factor	Gastric emptying scintigraphy	Wireless motility capsule	Breath test
Validated	+++	+++	+++
Standardized	++	+++	+++
Provides accurate and quantitative results	+++	+++	+++
Availability	+++	++	+
Ease of test performance/ need for specialized personnel	++	++	++
Patient inconvenience	++	++	++
Patient tolerance	+++	+++	+++
Radiation exposure	+	−/+	−
Expense	++	++	+

The scoring for each factor was based on the following descriptors:
Validated (+ = limited evidence relating test results to clinical presentation, diagnosis, and/or treatment; ++ = moderate evidence; +++ = significant evidence).
Standardized (+ = several distinct protocols for testing; ++ = a few protocols; +++ = a single uniform protocol).
Provides accurate and quantitative results (+ = testing provides findings that are predominantly qualitative in nature; ++ = testing provides some quantitative approximation of transit time; +++ = testing provides accurate transit time).
Availability (+ = test available at only a small number of centers; ++ = test available at modest number of centers; +++ = test widely available).
Test performance/need for specialized personnel (+ = testing is easy, protocols are easy, and minimal specialized training required for test performance; ++ = testing is moderately complicated with more complex protocols that require modest training; +++ = testing is highly specialized and requires advanced training).
Patient inconvenience (+ = minimal inconvenience in terms of travel or time commitment; ++ moderate inconvenience because more than one visit is required or test consumes several hours; +++ = significant inconvenience because of multiple test visits or long test times).
Patient tolerance (+ = significant discomfort during test preparation or testing; ++ = moderate discomfort during test preparation or testing; +++ = little discomfort during test preparation or testing).
Radiation exposure (− = no radiation exposure; + = a single radiograph or low dose radionuclide; ++ = a few radiographs or moderate radionuclide dosing; +++ = several radiographs or high doses of radionuclide).
Expense (+ = inexpensive; ++ = moderately expensive; +++ = very expensive).

Gastric emptying scintigraphy

Introduction A radiolabeled meal is widely used to measure gastric emptying (GE). Following its ingestion, the radioactivity measured from the stomach is directly proportional to the volume of meal remaining in the stomach. A consensus report has recommended a standardized meal and has provided normal values for conducting GE studies in a uniform manner.[1]

Indications A GE study is indicated for the evaluation of symptoms suggestive of gastroparesis such as early satiety, nausea, vomiting, bloating, postprandial fullness, and upper abdominal discomfort. A GE study is performed after excluding gastric outlet obstruction. Other indications include severe gastro-esophageal reflux disease unresponsive to acid suppressants, poorly controlled diabetes or to assess a generalized gut motility disorder.[2]

Study performance ^{99m}Tc-sulfur colloid labeled meal is commonly used to assess solid phase gastric emptying with scintigraphy. Liquid GE (usually labeled with indium) is often used to assess postsurgical conditions, as there can be discrepancy in liquid and solid gastric emptying after gastric surgery and/or vagotomy.[3,4] The test involves radiation which is increased with use of simultaneous evaluation of solid and liquid emptying.

The technical conduct, choice of collimator, windows for detection of the isotopes, quantitation and corrections of radioactivity for isotope decay and depth, caloric content of the meal, position (upright) and

timing of imaging (1, 2, and 4 h after meal – Fig. 1) are covered in the AMS-Society of Nuclear Medicine consensus document.[1] Standardization of testing includes overnight fast, avoidance of medications (e.g., prokinetics, opiates) that affect gastric emptying for 48–72 h prior to the test, and checking that fasting blood glucose is <280 mg dL^{-1} before starting the test. Subjects may require supplemental insulin, prior to and immediately after test completion. Smoking is not permitted during testing. The phase of menstrual cycle has a minor effect on GE and is generally disregarded in clinical practice.[5–7] Patients are permitted to sit, stand or walk between images.

Data analysis and endpoints The percentage retention at 4 h is more reproducible than data acquired during the first 2 h;[8] the 4-h analysis also detects more abnormal GE among symptomatic patients.[9] Gastric emptying is considered abnormally delayed if greater that 60% of the meal is retained at 2 h and/or greater than 10% at 4 h. Other measures of GE include time to 50% emptying ($T_{1/2}$) and a lag phase for solids.[10–12] However, receiver operating characteristic curves (ROC) showed that the percent emptied at 1, 2, and 4 h provided as much diagnostic information as the combined lag time and slope of the postlag emptying curve which require imaging every 15 min.[13,14]

Performance characteristics A comprehensive assessment of the performance characteristics of scintigraphic GE and the proportion emptied at 2 and 4 h, and $GET_{1/2}$ were evaluated in 37 healthy participants.[8] The inter-subject coefficient of variation (COV) at 1, 2, and 4 h were 62%, 29%, and 8% respectively and the

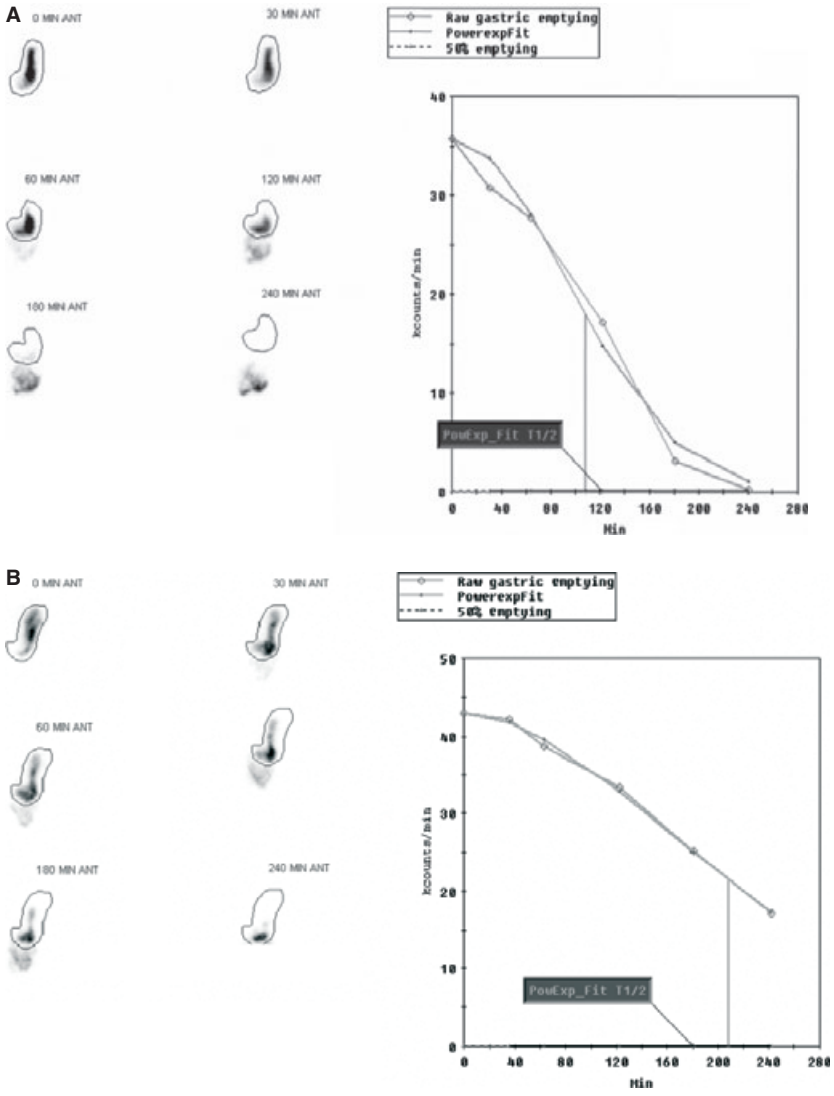

Figure 1 Gastric emptying scintigraphy: examples of (A) Normal gastric emptying (GE) showing anterior images at 0, 30, 60, and 120 min for solids labeled with Tc-99 meal, and (B) Delayed GE with retention of isotope in stomach at 2 and 4 h in a subject with gastroparesis.

intra-subject COV were 20%, 14%, and 4% respectively. The inter- and intra-subject COV for $GET_{1/2}$ were 30% and 14% respectively. The ~12% intra-subject COV for scintigraphic $GET_{1/2}$ was confirmed in two other studies.[15,16]

Responsiveness to treatment As validation of a diagnostic test for responsiveness requires effective therapies, the best assessment of GE responsiveness was shown with the use of cisapride and erythromycin. Gastric emptying was enhanced with cisapride and this was associated with improvement of symptoms of gastroparesis and dyspepsia.[17,18] Similarly, pharmacologic and clinical efficacy of erythromycin was demonstrated with scintigraphic GE.[19] A second level of pharmacological responsiveness was demonstrated by the predicted pharmacological effects of atropine (slowing) or erythromycin (acceleration).[20,21]

Clinical significance Delayed GE often forms the basis for a diagnosis of gastroparesis and helps to identify patients whose symptoms are likely to benefit from treatment.[22] The results of a GE study are also used to grade the severity of gastroparesis and provide guidance on selection of therapy,[22] and objectively measure the response to therapy.[19,23]

Strengths and confounding issues Studies demonstrate that delayed GE is found in 30–70% of patients with upper GI symptoms.[24] A delayed GE test confirms gastric dysmotility but does not prove that symptoms are due to gastroparesis. Both rapid and delayed GE can cause similar symptoms. Among tertiary care patients with endoscopy-negative upper GI symptoms (diagnosed as functional dyspepsia, postfundoplication, or rumination syndrome), GE was delayed in 14% and accelerated in 23%; among diabetics with such symptoms, GE was delayed in 46% and accelerated in 18% of patients.[25]

Criteria for rapid GE are less standardized but <38% retention at 60 min is suggestive of rapid GE.[1] The clinical role of liquid GE studies merits further study and is of growing interest. In spite of society guidelines, many centers continue to perform suboptimal studies (duration 1–2 h) that undermine the quality and utility of this test.

Recommendations Gastric emptying scintigraphy should be performed with a low-fat, egg white meal with imaging at 0, 1, 2, and 4 h to assess emptying of solids. The 1-h scan is used to detect rapid GE and the 2 and 4 h are used to detect delayed gastric emptying. It is widely available, validated and reproducible and involves a small amount of radiation. It is recommended for the evaluation of subjects with suspected gastroparesis and/or dumping syndrome. In clinical practice, the test is hampered by a lack of uniform methodology across centers.

Wireless motility capsule

Introduction The wireless motility capsule (WMC) is a single-use, orally ingested, non-digestible, data-recording capsule that measures pH, pressure, and temperature throughout the GI tract. This capsule is capable of measuring regional and whole gut transit including gastric emptying time (GET), small bowel transit time (SBTT), colonic transit time (CTT), and whole gut transit time (WGTT).

Indications A WMC test is approved by the US Food and Drug Administration (FDA) and indicated for the evaluation of suspected delayed gastric emptying (gastroparesis) in disorders such as idiopathic or diabetic gastroparesis and functional non-ulcer dyspepsia.

Study performance The WMC (SmartPill®; SmartPill Corporation, Buffalo, NY, USA), measures 11.7 mm × 26.8 mm in size and houses sensors for pH (range = 0.05–9.0), pressure (0–350 mmHg) and temperature (25–49 °C), and requires activation using an activation fixture. The WMC is ingested immediately following a standardized meal comprising of a nutrient bar (calories = 255; fat = 2.2%) and 50 mL water. Subjects are not permitted to eat for the next 6 h while GE of WMC is assessed. For assessment of WGTT, the receiver is worn on the waist for 3–5 days during which time the subject is free to ambulate and is instructed to push the event button and to keep a diary of events (e.g., meals, sleep, bowel movements). The data recorder is returned and the information is downloaded via a docking station for analysis.

Data analysis and endpoints Gastric emptying time, SBTT, CTT, and WGTT are defined using specific pH and temperature profiles.[26–28] Gastric emptying time is defined as the duration of time from capsule ingestion to an abrupt pH rise (usually >3 pH units, see Fig. 2) as the capsule passes from the acidic antrum to the more alkaline duodenum.[26] The WMC usually requires a phase 3 migratory motor complex to pass into the small bowel.[29]

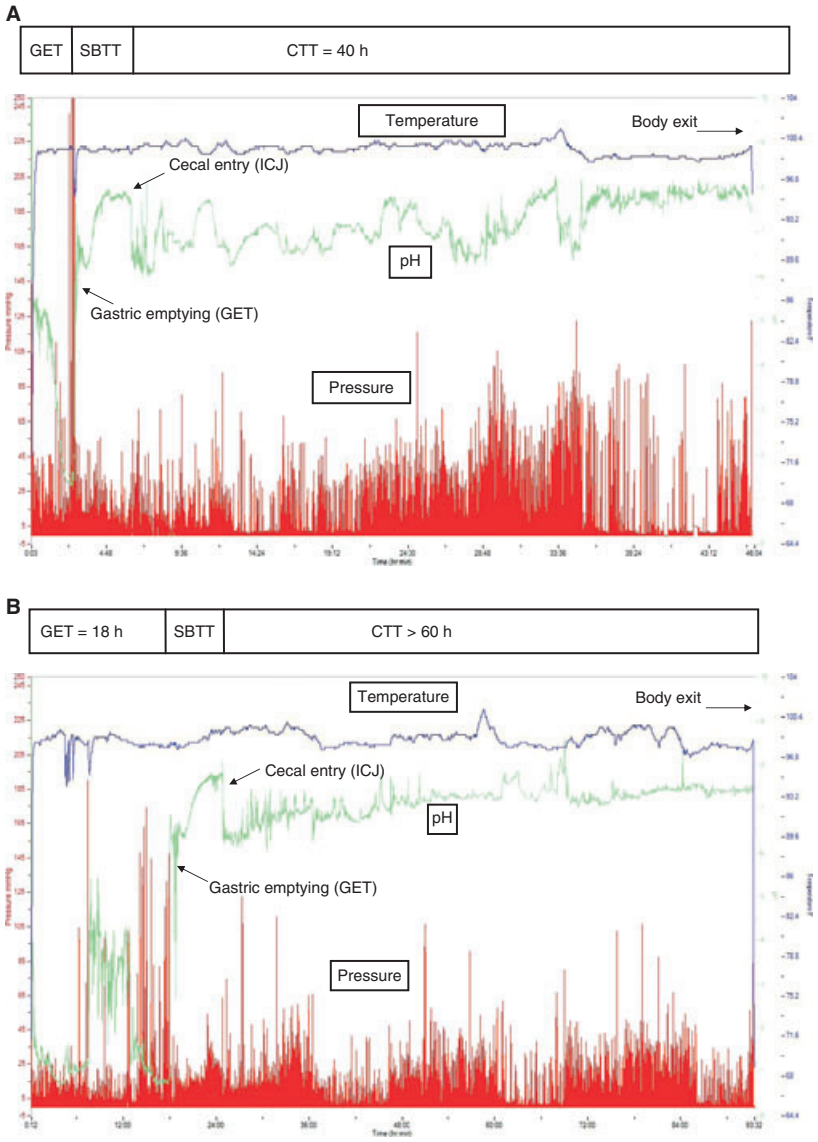

Figure 2 Wireless motility capsule: (A) This figure displays wireless motility capsule (WMC) profiles from a healthy subject and shows normal gastric emptying, normal small bowel transit and normal colonic transit time, and (B) delayed gastric emptying and delayed colonic transit and delayed whole gut transit time in a subject with symptoms of gastroparesis and constipation.

Performance characteristics In 87 healthy and 61 gastroparetic individuals who underwent simultaneous WMC and scintigraphic measurement of GE, the authors reported correlation coefficient of 0.73 relative to the 4-h scintigraphic data and 0.63 relative to the 2-h data.[26] The sensitivity and specificity of WMC in detecting delayed GE based on 4 h scintigraphic data were 0.87 and 0.92, respectively. Utilizing this analysis, the WMC cut-off point for delayed GET that provides an optimum balance of sensitivity and specificity for clinical use was 300 min.[26] The estimated inter-subject COV for GET with WMC in health and gastroparesis were 28% and 34% respectively and there was no difference.[26]

Responsiveness to treatment Pharmacological responsiveness in healthy subjects was shown by the ability of WMC to detect acceleration of gastric emptying induced by erythromycin and slowing of gastric emptying by morphine.[30]

Clinical significance This is discussed below in the colonic transit assessment of WMC section.

Strengths and confounding issues The WMC provides a means of measuring transit free of radiation exposure in ambulatory setting, and has the advantage of simultaneously measuring GET, SBTT, CTT and WGTT and providing a pressure activity profile

throughout the gut further defining conditions with altered GI motility.[31,32] The disadvantages include ingestion of a large capsule, and wearing/returning a data receiver for up to 5 days if WGTT is being assessed. There is a risk of capsule retention [20/6000 cases (0.33%) as of January 2010] which required endoscopic removal in two cases. Its use is contraindicated in patients with pseudo-obstruction, ileus, and gastric bezoar.

Recommendations The WMC is recommended for an assessment of gastric emptying and regional and whole gut transit time in individuals with suspected gastroparesis and symptoms of upper GI dysmotility. It is particularly useful for testing individuals with suspected alterations of GI motility in multiple regions.

Gastric emptying breath test (GEBT)

Introduction A test meal labeled with a stable (non-radioactive) isotope (^{13}C) can be used to measure gastric emptying. The ^{13}C containing moiety is typically the medium chain fatty acid, ^{13}C-octanoic acid,[16,33] or the edible blue-green algae, ^{13}C-*Spirulina platensis*.[34] When these substances are baked with egg, the ^{13}C does not dissociate, and it empties from the stomach at the same rate as other solids. Subsequently, the ^{13}C containing substrate is either absorbed directly (octanoic acid) or digested and then absorbed (*Spirulina platensis*). It then becomes part of the body's bicarbonate pool, and is finally excreted by the lungs as $^{13}CO_2$. Although there are multiple steps in this process, the rate limiting step for $^{13}CO_2$ excretion is gastric emptying.

Indications The ^{13}C-*Spirulina platensis* GEBT is indicated for measuring gastric emptying of solids in adults. A FDA application has been submitted.

Study performance After an overnight fast, the ^{13}C-labeled test meal (e.g., 100 mg ^{13}C-*Spirulina platensis*, 27 g freeze-dried egg mix, six saltine crackers, and 180 mL of water) is consumed. Breath samples are collected at fixed time points (e.g., 45, 150, 180 min), and mass spectrometry is used to determine the $^{13}CO_2/^{12}CO_2$ ratio in the samples. The breath samples are stable for months.[35] Less expensive bench-top infra-red devices have also been validated.[36]

Data analysis and endpoints Breath testing is an indirect measure of GE (Fig. 3).[16] Multiple mathematical analysis methods have been proposed for the interpretation of the breath test metrics,[33,34,37,38] but the linear regression method had the highest concordance correlation coefficient with scintigraphic $T_{1/2}$.[39] In a large study of 124 patients, linear regression was used to compare GE breath test (time points 45, 150, and 180 min) to scintigraphy, with accurate detection of accelerated or delayed emptying.[34]

Performance characteristics The intra-subject COVs for scintigraphy and the ^{13}C-*Spirulina* GEBT were highly comparable (3–4% different) at all time points from 45 to 180 min in health. Inter-subject COVs at each time for the GEBT and scintigraphy were typically ~1–4% lower than intra-subject COVs. Individual breath samples at 45, 150, and 180 min predicted emptying category (delayed, normal or accelerated): at 80% specificity, 45- and 180-min samples combined were 93% sensitive for identifying accelerated GE, and 150- and 180-min samples combined were 89% sensitive for delayed GE.[34] Intra- and inter-subject variations of measurements of GE with the ^{13}C-octanoic acid GEBT were not significantly different from the variations observed with scintigraphy.[40]

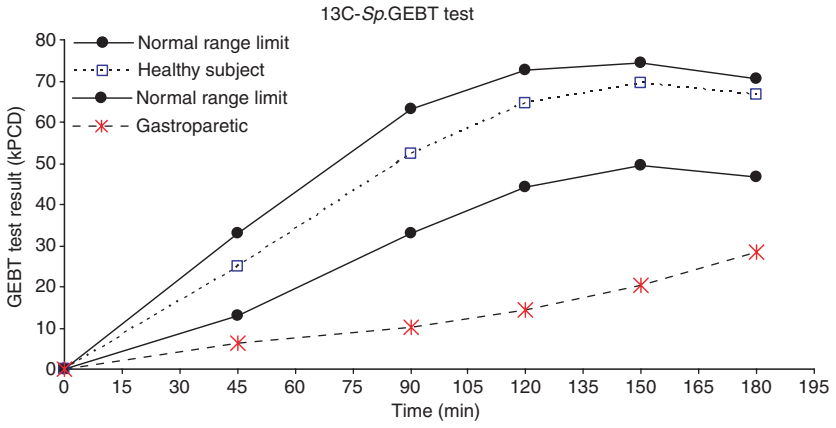

Figure 3 Gastric emptying breath test: Gastric emptying curves in a healthy subject and in a gastroparetic subject showing percent dose ^{13}C excreted (kPCD) at different time points following ingestion of a standardized ^{13}C-*Spirulina platensis* gastric emptying breath test meal. The normal range is also shown.

Responsiveness to treatment Several studies have documented the effect of pharmacological agents on the gastric emptying parameters in health and diseases such as diabetes mellitus.[37,41]

Strengths and confounding issues No radiation is involved and the test is simple and does not require any special equipment on-site, and can be performed in the office or bed side. There are pitfalls in the interpretation of this test. Theoretically, ^{13}C-*Spirulina platensis* requires digestion before absorption, and intestinal mucosal disease, pancreatic or biliary insufficiency may interfere with the test. ^{13}C-octanoic acid breath test performance should not be affected by these factors; as has been shown for cumulative $^{13}CO_2$ excretion in liver, kidney, lung disease.[42,43]

Recommendations ^{13}C-GEBT is a simple, safe, radiation-free and validated test for assessing gastric emptying. It is used clinically in some centers in Europe, but is not presently available for clinical use in USA.

Other techniques of measurement of gastric emptying

Ultrasonography Transabdominal ultrasonography measures emptying, and gastroduodenal flow.[44] Serial changes of antral cross-sectional area can provide an index of GE. Ultrasound determination is operator dependent and has proven reliable only for measurement of liquid emptying. Testing may be difficult in obese individuals. Ultrasonography is most commonly used in research settings. Duplex sonography can quantify transpyloric flow of liquid gastric contents and accommodation in the proximal stomach whereas 3D ultrasonography can measure gastric volume and emptying.[45]

Magnetic resonance imaging Magnetic resonance imaging has been used to measure emptying, wall motion, and gastric volume, the latter being an index of gastric accommodation. Transaxial abdominal scans are generally obtained in the supine position every 15 min before and after a predominantly liquid meal applying a spin-echo technique with T1 weighted images.[46] The specialized equipment and expense, and the supine position have limited its role to research settings.

ASSESSMENT OF SMALL BOWEL TRANSIT

Altered transit of food and chyme through the small bowel, particularly stasis due to an underlying myopathy (scleroderma) or neuropathy (diabetes) can cause significant symptoms. Several tests are available for the assessment of SBTT, and their pros and cons are discussed in Table 2. They may be an alternative to manometry, an invasive test with limited availability. Transit measurement is a helpful tool for physiological and pharmacodynamic studies of small bowel motor function.

Table 2 Pros and cons of tests for the assessment of small bowel transit

Factor	Breath tests	Scintigraphy	Wireless motility capsule
Validated	++	++	+
Standardized	+	++	+++
Provides accurate and quantitative results	++	++	+++
Availability	++	+	++
Test performance & need for specialized personnel	++	++	++
Patient inconvenience	++	++	++
Patient tolerance	++	+++	+++
Radiation exposure	–	++	– or +*
Expense	+	++	++

*Depends on whether capsule retention is suspected.

Overall indications

The main indication for assessment of SBTT is the evaluation of subjects with unexplained nausea, vomiting, bloating, visible distention, or other manifestations of small intestinal bacterial overgrowth (SIBO) or dysmotility.

Breath tests

Introduction Breath testing to quantify orocecal transit time (OCTT) involves ingesting a non-digestible carbohydrate substrate like lactulose which upon contact with enteric bacteria is metabolized to liberate gases (hydrogen, methane, carbon dioxide etc.) which diffuse across the mucosa, are transported to the lungs, and expired in breath. Orocecal transit time reflects gastric and small bowel transit.

Study performance End-expiratory breath samples are acquired at baseline and at regular intervals after consuming 10 g of lactulose.[47] Orocecal transit time is defined as time interval between ingestion and when sustained (5–10 parts per million) rises in hydrogen are detected by gas chromatography (Fig. 4).

Data analysis, endpoints, and performance characteristics Orocecal transit times range from 53 to 208 min

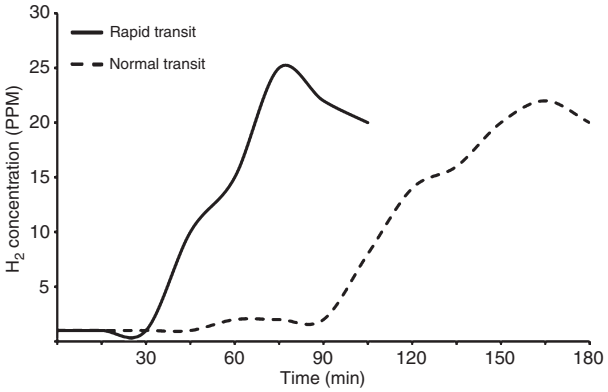

Figure 4 Lactulose hydrogen breath test: This shows examples of a subject with a normal lactulose hydrogen breath test and a subject with accelerated (abnormal) orocecal transit time.

in health, with high intra-subject (14–39%) and inter-subject (up to 56%) variabilities. Mean inter-individual COV (21 healthy subjects) was 18.5%, 30%, and 28% with doses of lactulose of 10, 15, and 20 g respectively.[48] Orocecal transit time with breath tests show variable correlation with barium radiography or scintigraphy. The correlation coefficients range from 0.31 to 0.95.[49] The differences in transit times between breath tests and scintigraphy are in part due to the time required for substrate metabolism and hydrogen transport to the lungs.

Other proposed methods include measuring breath $^{13}CO_2$ after lactose-^{13}C-ureide;[50] this has been tested with different meal substrates.[51] With duodenal infusion of the substrate, it is possible to selectively quantify SBTT.

Clinical significance Breath testing has been used to quantify OCTT in health and disease: accelerated transit in lactose intolerance and other diarrheal conditions, and delayed transit in constipation, inflammatory/autoimmune disorders (Crohn's disease, celiac disease, scleroderma), hormonal conditions (pregnancy, hypothyroidism), cystic fibrosis, and neurologic disease. Prokinetic drugs and serotonin reuptake inhibitors accelerate OCTT, whereas opiates, contraceptives, and tricyclic agents retard transit.

Strengths and confounding issues Strengths of breath testing to assess OCTT include ease of performance, low expense, and safety which permits use in populations (e.g., pregnancy) in whom scintigraphy would be contraindicated. Limitations of breath testing that confound its utility to measure OCTT include identification of the peak, potential acceleration of SBTT and deceleration of GE with lactulose, an osmotic laxative,[47,49] and significance of the peak as a measure of transit in the setting of potential SIBO including short bowel syndrome, or those with ileal pouches, prior gastric retention, and irritable bowel syndrome.[47] Early hydrogen peaks in SIBO can obscure hydrogen production from colonic metabolism, making OCTT determination impossible. Finally, exercise, smoking and exhalation technique can affect results of testing.[47–49]

Recommendations The orocecal transit time with lactulose provides semi-quantitative assessment of small bowel transit and may be useful in subjects for whom more precise methods are not available, too expensive, or too dangerous. Its shortcomings outweigh its benefits for assessment of small bowel transit in clinical practice.

Scintigraphy

Introduction Assessment of SBTT using radionuclide scintigraphy is usually performed as part of a whole gut transit study.

Study performance The test involves ingestion of either a liquid (water)[2,52] or solid (resin beads or meal),[13,53,54] material labeled with ^{111}In or ^{99m}Tc, and obtaining sequential scans over several hours.

Data analysis and endpoints Small bowel transit time can be calculated in several ways,[55] but most commonly as the time for 10% or 50% of the activity to arrive at the terminal ileum or cecum, after correcting for GE.[56] A valid surrogate for the 10% SBTT is the percent of the meal filling the colon at 6 h.[13] Thus, a study can be deemed normal or abnormal, based on the percentage of activity arriving at these regions within a specified time, typically 6 h.

Performance characteristics Normative data are limited (n < 30 subjects), with wide ranges for SBTT that are method-dependent.[54,57,58] Consequently, the test is only diagnostic if extreme values are obtained. Rapid SBTT has been defined as >70% colonic filling at 6 h,[13] or cecal arrival time of <90 min.[2] Delayed SBTT has variably been defined as colonic filling of <11% or <40% at 6 h.[2,13] Neither age nor gender appear to influence SBTT,[54,58] but there is significant inter- (30%) and intra-subject (19%) variability for the colonic filling at 6 h (CF6), a surrogate for SBTT.[8] In a study of 95 participants [healthy and irritable bowel syndrome (IBS)], the mean CF6 was 51 ± 3% and the estimated inter-subject COV was 56%.[59] However,

CF6 is a measure of OCTT and could be significantly influenced by GE rate.

Responsiveness to treatment Responsiveness of SBTT to treatment was shown in studies of the effect of cisapride in patients with gastroparesis and chronic intestinal dysmotility[60,61] and of tegaserod in patients with IBS-constipation.[62]

Clinical significance Identification of delayed SBTT has been shown to alter both initial diagnosis and clinical management.[63] However, a confounder is that delayed colonic transit will delay SBTT and therefore SBTT needs to be interpreted with caution in patients with delayed colonic transit or constipation. Data on clinical outcomes are limited.

Strengths and confounding issues Scintigraphy provides physiological and quantitative information. However, the technique is not standardized, the normal range is wide, and interpretation potentially compromised with abnormal gastric or colonic transit. The gamma camera costs, radiation, need for prolonged scanning time, and difficulty in delineating anatomy are other drawbacks.

Recommendations Scintigraphy is recommended for detection of altered small intestinal transit in subjects with suspected diffuse GI motility disorder but is available in a limited number of centers.

Wireless motility capsule

Introduction and indications Measurement of SBTT has been performed with WMC.[27,28,64,65] It is indicated for detection of generalized dysmotility or as part of evaluation of WGTT.

Study performance Measurement of SBTT is based upon validated stereotypical changes in pH profile, namely a rise in pH from acid to near neutral as the capsule exits the stomach, and a fall of >1 pH unit from the alkaline environment of the terminal ileum as it passes into the large bowel.[66,67] Time between the two events is taken as SBTT (Fig. 2).

Data analysis, endpoints, and performance characteristics Large normative data sets are available.[27,28,68] Median SBTT has been reported as 4.6 h (4.0–5.9 h, 25th and 75th percentiles),[28] although measurement is influenced by timing of capsule ingestion in relation to the test meal. Small bowel transit time in both gastroparetic and constipated subjects has been published.[27,28,64] The interindividual COV in SBTT for health, gastroparesis and constipation were 33%, 33%, and 37% respectively.

Clinical significance Small bowel transit time is prolonged in some patients with symptoms of upper and lower GI dysmotility,[69] but its clinical utility is as yet unclear.

Strengths and confounding issues The WMC overcomes the need for radiation and is a standardized test. Furthermore, the subject is ambulant and recordings can be carried out at home. Determination of SBTT is not possible in some subjects (~5–10%), as pH landmarks cannot be accurately identified.[27,64]

Recommendations The WMC is a standardized, radiation-free method for assessment of small bowel transit and is recommended for clinical use to facilitate detection of small bowel dysfunction in subjects with a more generalized GI motility disorder.

Other techniques for assessment of SBTT

Alternative methods include the use of video capsule endoscopy[70] or magnetic pill.[71] For capsule endoscopy, analysis of endoluminal visual data, using computer vision techniques, allows for recognition of intestinal contractile patterns. Small bowel transit time is determined by visual detection of capsule exit from the stomach and arrival in the cecum.[70]

Capsules have the advantage of simplicity, minimal discomfort and performance in ambulatory setting. Their drawbacks include that capsules are likely to empty from the stomach with resumption of fasting pattern of motility thereby providing data on small bowel transit during fasting and that their movement may not reflect that of chyme, and their retention in stomach or small bowel if lumen is obstructed may limit its use.

ASSESSMENT OF COLONIC TRANSIT

Disorders of colonic motility typically present with constipation or diarrhea, and often affect colonic transit time (CTT). The availability of a simple, safe and reliable method to quantify CTT is therefore of significant diagnostic importance in the evaluation of these patients, and may help to select appropriate therapies. Two methods of assessing CTT, radioopaque markers and colonic scintigraphy, are well established; a third procedure involving a WMC has

Table 3 Pros and cons of tests for the assessment of colonic transit

Factor	Radioopaque markers	Colonic scintigraphy	Wireless motility capsule
Validated	+++	+++	+++
Standardized	+	++	+++
Provides accurate and quantitative results	+ or ++*	+++	+++
Availability	+++	+	++
Test performance & need for specialized personnel	++	+++	++
Patient inconvenience	+ or ++*	+++	++
Patient tolerance	+++	+++	+++
Radiation exposure	+ or ++ or +++*	++	− or +†
Expense	+	++	++

*Depends on technique of ROM test; †If capsule retention is suspected.

been recently validated. The pros and cons of common techniques are discussed in Table 3.

Radioopaque markers

*Introduction*Measurement of CTT using radioopaque markers (ROM) was first described in 1969 and has been widely adopted.[72]

Indications Radioopaque marker testing is indicated to differentiate between normal and slow colonic transit in patients with constipation, to assess segmental transit times in patients with delayed total colon transit, and to assist in the evaluation of unexplained diarrhea.

Study performance Radioopaque markers are plastic beads or rings that are usually ingested in a capsule (Sitzmarks®; Konsyl Pharmaceuticals, Easton, MD, USA) or with a meal. Abdominal X-rays are performed at predetermined times and the number of retained markers is counted (Fig. 5). Radioopaque markers test measures WGTT. However, as most of the WGTT reflects passage through the colon, the test is an approximation of CTT.

Data analysis and endpoints Different protocols for ROM measurement of CTT have been described which affects analysis and interpretation.

1 A single capsule containing 24 markers followed by a single abdominal X-ray on day 5 (120 h later). Retention of ≥5 markers (Fig. 5) is abnormal.[27] There is limited radiation exposure; however no quantitative information on CTT is provided.

2 Twenty-four markers of similar or different shapes are ingested daily for 3–6 consecutive days and X-rays are obtained on day 4 and 7 (or only on day 7).[73–76]

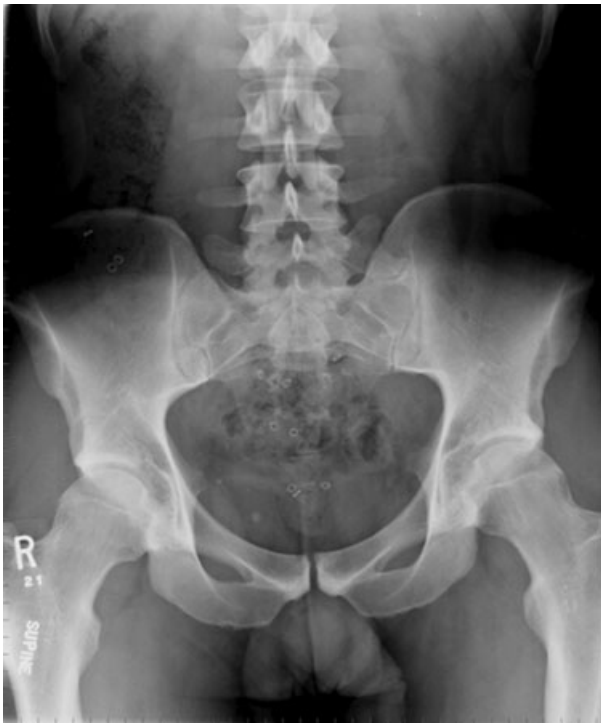

Figure 5 Radioopaque marker colonic transit test: This X-ray was taken at 120 h after ingestion of a single capsule containing 24 radioopaque markers in a subject with chronic constipation. It shows retention of several ring-shaped plastic markers indicating delayed colonic transit.

Transit time is quantitated because equilibrium between daily marker output and input is achieved by the time radiographs are taken.

3 A single dose of markers is ingested and serial X-rays are obtained every 24 h until no markers are visible. This method is time consuming, inconvenient and produces greater radiation exposure.[72]

Performance characteristics Normative data for CTT from a large number of ROM studies are available for adults and children.[74–77] In most studies, the mean CTT is 30–40 h with an upper limit of normal of 70 h in mixed populations. Women have longer maximal CTT (70–106 h) compared to men (50 h).[77] In one study of regional colonic transit, total CTT was 35 ± 2 h (mean ± standard error) with 11.3 ± 1.1 h for the right colon, 11.4 ± 1.4 h for the left colon, and 12.4 ± 1.1 h for the rectosigmoid.[75] Thus, the inter-subject COV is 51.3%. In a second study, overall CTT in men was 31 h and in women 36 h.[76] Thus, the estimated inter-subject COV in men is 19.4% and in women 42%.[76] Differences in CTT reported between studies may reflect differences in age and gender ratios and methodology among studies. Some studies have observed fair

degrees of reproducibility of CTT measurements on repeated study with mean difference 0.4 ± 0.8 days (mean ± SD), and 0.4 days respectively.[73,76] Intra- and inter-observer variabilities are low; the coefficient for intra-observer repeatability and limits of agreement between two observers were found to vary between 2 and 4 markers.[78] This was further improved when a colonic barium trace was added.[78] Colonic transit time measured by ROM and scintigraphy methods are similar, even though the center of mass of the ROMs propagates slightly ahead of the scintigraphic tracer.[79] Likewise, correlations between CTT with ROM and the WMC are good.[27]

Responsiveness to treatment The ROM technique has been used in several pharmacotherapeutic studies to asses the effects of drugs on altering colonic transit. Acceleration of CTT with ROM was associated with improvement in bowel symptoms in constipated patients in several clinical trials that evaluated polyethylene glycol,[80] tegaserod,[81] and prucalopride.[82]

Clinical significance Radioopaque markers measurements of CTT are widely used in clinical practice and research; they may distinguish constipation subgroups.[73,74] However, ~60% of patients with dyssynergic defecation have delayed CTT.[83] Hence, anorectal physiological tests are required to definitively identify subjects with slow transit constipation alone. The ROM test quantified CTT with reasonable accuracy in patients with diarrhea secondary to bile acid malabsorption.[84]

Strengths and confounding issues The ROM methods are widely available, safe, repeatable, non-invasive, and inexpensive. The main drawbacks of ROM testing are lack of standardization between centers, errors with interpretation of test results, inconvenience and lack of patient compliance (e.g., intake of multiple capsule or attendance for X-rays), and radiation exposure (Table 3). Future validation studies are needed to standardize the number of ROMs ingested, the timing of X-rays, the methods of reporting, and to develop normative values and performance characteristics with a consensus method. Such data are not available and hence interpretation of results is still suspect despite 4 decades of use in clinical practice.

Recommendations The ROM study is recommended for clinical evaluation of CTT in subjects with constipation and irritable bowel syndrome. It is relatively inexpensive and widely available.

Colonic transit scintigraphy

Introduction Colonic transit scintigraphy (CTS) is performed following ingestion of a radioactive meal or labeled non-absorbable charcoal to examine the transit of meal residues through the colon. It has been used as a biomarker in drug development for disorders of colonic motor activity.[85] The test offers reproducible and accurate performance across a spectrum of disorders, linking colonic transit measurements to symptoms and disease processes, and demonstrating response to treatment.

Indications Test is indicated to measure whole gut and regional colonic transit in patients with suspected colonic motility disorders or more diffuse disorders involving the stomach or small intestine.[2,85,86]

Study performance Two methods have been described: Temple University[2,56] assesses colon transit of ^{111}In DTPA-labeled water consumed in a standard solid-liquid meal for gastric scintigraphy and Mayo Clinic[87,88] uses a capsule (containing ^{111}In adsorbed on activated charcoal) coated with the pH-sensitive polymer methacrylate that dissolves in the alkaline terminal ileum, releasing the radioisotope into the lumen (Fig. 6).

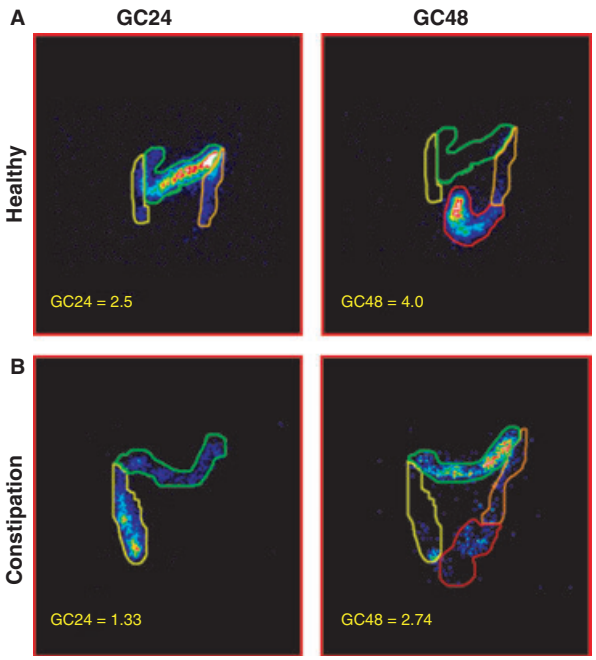

Figure 6 Colonic transit scintigraphy: This shows examples of colonic transit scintigraphic images (A) from a healthy subject with a normal geometric center (GC) count at 24 and 48 h and (B) from a subject with constipation showing abnormally low values for geometric center of a isotope meal at 24 and 48 h due to retention of radioisotope in the colon indicating delayed colonic transit.

Data analysis and endpoints Two end points are used to summarize colonic transit: (i) a numeric value of overall colonic transit, expressed as the geometric center (based on seven regions at Temple, five regions at Mayo), and (ii) ascending colon emptying summarized as the $T_{1/2}$ (time for 50% emptying). Concurrent validity has been demonstrated relative to radioopaque markers.[79,88]

Performance characteristics These have been appraised in health and IBS. In 21 healthy volunteers who underwent CTS twice, 3 weeks apart, interindividual COV were 37% at 24 h and 24% at 48 h, while intraindividual COVs were 28% and 14%, respectively.[89] In a study of healthy individuals and IBS-Constipation (IBS-C) patients, COV_{intra} was 31% at 24 h and 27% at 48 h over a short-term period of <3 weeks and 38% at 24 h and 30% at 48 h over a median interval of 2 years.[59] The COV reflects the known variation in stool frequency and consistency in IBS-Diarrhea (IBS-D) patients. No significant differences were observed in replicate studies in IBS-C and IBS-Mixed (IBS-M). One grade change in Bristol stool consistency scale is associated with a 0.6–0.7 change in colonic geometric center at 24 or 48 h.[59]

Responsiveness to treatment Pharmacodynamic CTS studies have correctly predicted degrees of efficacy (using symptom-based end points) in phase IIB or III trials of medications with diverse mechanisms of action, including alosetron, tegaserod, prucalopride, linaclotide, and lubiprostone[85] demonstrating therapeutic responsiveness.

Clinical significance Colonic transit scintigraphy quantifies slow colonic transit in patients with constipation and can influence patient management.[2,90] Additionally, CTS can determine if the motor abnormality is diffuse or localized to a specific colonic region.[2,88,90,91] Colonic transit scintigraphy identified accelerated colonic transit in patients with IBS-D and about 20% of patients with IBS-C.[90]

Measurement of WGTT also helps direct treatment. If WGTT is delayed, prokinetic treatment may be indicated. With severe slow transit constipation, responses to colectomy are better in patients with isolated colonic dysfunction than in those with associated gastric and/or small bowel transit delays.[92] If WGTT is normal, patient education, dietary advice, and osmotic laxatives may be more useful than prokinetics or surgery. The clinical utility of scintigraphic testing was demonstrated in 104 patients including 73 patients with constipation as initial clinical diagnoses.[2] Colonic transit scintigraphy changed the initial clinical diagnosis in 47/104 (45%) and altered patient management in 70/104 (67%) of the patients.

Strengths and confounding issues There is biologic plausibility, stable performance characteristics, and association with the clinical alteration of bowel function in diseases that affect colonic motility that all support use of CTS as a marker to validate new treatments and to help direct patient care.[2,85]

Recommendations Colonic transit scintigraphy is recommended for assessing colonic transit in patients with constipation or diarrhea but is available in a limited number of centers.

Wireless motility capsule

Introduction The WMC is a new technique of assessing colonic and whole gut transit.

Indications The WMC test is indicated in patients with suspected bowel disorders including chronic constipation and to distinguish slow from normal colonic transit. Measurement of combined small and large bowel transit time (SLBTT) is performed as a surrogate measure of colonic transit in chronic constipation when CTT alone cannot be determined.

Study performance The WMC transit protocol is discussed above under gastric emptying (Fig. 2A,B).

Data analysis and endpoints Cecal entry is defined as a distinct, sustained (>10 min) pH drop of >1 unit that occurs ≥30 min after gastric emptying. Colonic transit time is defined as the time between cecal entry and capsule exit from the body (loss of signal and/or an abrupt temperature drop). Small and large bowel transit time is defined as the time between gastric emptying and body exit, and is calculated when cecal entry cannot be detected (5% of cases).

Performance characteristics Large studies have confirmed its performance characteristics and utility in quantifying CTT when compared to conventional tests,[26,27,64] (Table 3). There was good agreement between the WMC and ROM transit results. The inter-subject COV for CTT was 68, and 67% in health and constipation respectively. Correlation coefficients of CTT by WMC relative to ROM expelled on day 2 and day 5 were 0.74 and 0.69 in constipation, and 0.70 and 0.40 in healthy controls.[27]

In a prospective study, GET, CTT and WGTT measured by WMC were slower in 78 constipated

subjects (Rome II) *VS* 87 healthy controls ($P < 0.01$).[27] The diagnostic accuracy and specificity of CTT (WMC) to predict constipation from ROC were 0.73 and 0.95, respectively; these were comparable to values of 0.71 and 0.95 for day 5 ROM. Thus, WMC correlated well with ROM and discriminated normal from slow colonic transit.

In 158 patients with chronic constipation who underwent simultaneous CTT measurement using ROM and WMC,[64] the positive device agreement between WMC and ROM for delayed transit was ~80% and negative device agreement (normal transit) was ~91%. Correlation coefficients between ROM *VS* WMC for CTT and SLBTT were 0.71 and 0.70, respectively. There was 87% agreement validating WMC relative to ROM in differentiating slow *VS* normal CTT in constipation. Moreover WMC and scintigraphic WGTT show good correlation.[93] The intra-class correlation coefficients for GET, SBTT, CTT, and WGTT measurements in a combined group of 45 healthy, gastroparetic and constipated subjects were 1.0, 0.93, 0.99, and 1.0 respectively.[94] There was excellent inter-rater agreements for regional and WGTT between three independent raters with varying degrees of experience.[94] Another study showed that 80% of healthy subjects remain within the normal or abnormal range when test is repeated with a COV of 60%.[95] In two studies, Bristol stool form but not stool frequency showed modest correlations ($R = 0.39$) with WMC measures of WGTT and CTT in mixed populations confirming the need for objective testing when precise estimates of gut transit are necessary.[64,96]

Clinical significance The diagnostic utility of WMC *VS* conventional motility tests was assessed in 86 patients stratified into upper GI (UGI, $n = 36$), and lower GI (LGI, $n = 50$) dysfunction.[69] In addition to confirming a clinical suspicion and good device agreement, significant new diagnostic information was obtained with WMC in the UGI ($P = 0.001$) and LGI ($P = 0.006$) groups when compared to conventional motility tests. Moreover WMC detected a motility disorder affecting more than one region in 51% of subjects.[69,97] It influenced management in 30% of LGI and 88% of UGI subjects.[69] In another study, WMC lessened the need for further invasive motility tests.[97]

Strengths and confounding issues The WMC is well-tolerated, exhibits good compliance, and measures CTT and WGTT under ambulatory conditions without radiation exposure. However, it requires physician training for interpretation, and device failure is reported in ~3% of cases. It has not yet been tested for colonic responsiveness to pharmacological agents.

Recommendations The WMC is a validated and standardized test. It is recommended for assessment of colonic transit time in subjects with constipation and those with suspected colonic disorders. It also provides measurements of regional and whole gut transit.

CONCLUSIONS

A variety of tests are available to assess GI transit in the clinical evaluation of patients with symptoms of dysmotility. Measurements of gastric emptying time using scintigraphy of a radiolabeled solid or liquid meal or a WMC are useful in clinical practice for assessment of gastric emptying. ^{13}C-GEBT may also be useful but is presently not available for clinical use in USA. Measurements of small bowel transit time using WMC and scintigraphy provide useful assessments of altered small bowel function. Assessment of orocecal transit time with lactulose breath test is simple but is less accurate. Measurements of colonic transit time have been traditionally performed with radioopaque marker test. Recently WMC and colonic scintigraphy have been validated for detection of both abnormal colonic transit and whole gut transit. All three modalities are clinically useful for detection of altered colonic transit, although scintigraphy is only available in limited centers.

ACKNOWLEDGMENTS

We thank Mrs Lori Ennis, Mrs Cindy Stanislav and Mrs Jessica Valestin for their excellent assistance with this work and in the preparation of this document.

CONTRIBUTING AUTHORS

Michael Camilleri, William L. Hasler, Alan Maurer, Henry Parkman, Richard Saad, Mark Scott, Magnus Simren, Edy Soffer, Larry Szarka; all authors have played an equally important role in study concept and design, data analysis and interpretation, manuscript preparation, critical revision, important intellectual content and final approval. Guarantor: Satish S. C. Rao: Study concept and design, data analysis and interpretation, manuscript preparation, critical revision, important intellectual content and final approval.

COMPETING INTERESTS

Satish Rao: Advisory board member and has received research funding from the SmartPill Corporation. Michael Camilleri: Received research funding from the SmartPill Corporation. William L. Hasler: Received research funding and Consultant for SmartPill Corporation. Alan H Maurer: Nothing to disclose. Henry P Parkman: Advisory board member and has received

research funding from the SmartPill Corporation. Richard Saad: Received research funding from the SmartPill Corporation. Mark S Scott: Received research funding from the SmartPill Corporation. Magnus Simren: Nothing to disclose. Edy Soffer: Received research funding from the SmartPill Corporation. Lawrence Szarka: Received research funding from Advanced Breath Diagnostics, LLC.

REFERENCES

1 Abell T, Camilleri M, Donohoe K *et al.* Consensus recommendations for gastric emptying scintigraphy: a joint report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. *Am J Gastroenterol* 2007; **102**: 1–11.
2 Bonapace ES, Maurer AH, Davidoff S, Krevsky B, Fisher RS, Parkman HP. Whole gut transit scintigraphy in the clinical evaluation of patients with upper and lower gastrointestinal symptoms. *Am J Gastroenterol* 2000; **95**: 2838–47.
3 Couturier O, Bodet-Milin C, Querellou S, Carlier T, Turzo A, Bizais Y. Gastric scintigraphy with a liquid-solid radiolabelled meal: performances of solid and liquid parameters. *Nucl Med Commun* Nov 2004; **25**: 1143–50.
4 Ziessman H, Ankit C, Clarke J, Ramos A, Wahl R. The added value of liquid gastric emptying compared with solid emptying alone. *J Nucl Med* 2009; **50**: 726–31.
5 Datz F, Christian P, Moore J. Gender-related differences in gastric emptying. *J Nucl Med* 1987; **28**: 1204–7.
6 Gill R, Murphy P, Hooper H, Bowes K, Kingma Y. Effect of the menstrual cycle on gastric emptying. *Digestion* 1987; **36**: 168–74.
7 Knight LC, Parkman HP, Brown KL *et al.* Delayed gastric emptying and decreased antral contractility in normal premenopausal women compared with men. *Am J Gastroenterol* 1997; **92**: 968–75.
8 Cremonini F, Delgado-Aros S, Talley NJ. Functional dyspepsia: drugs for new (and old) therapeutic targets. *Baillieres Best Pract Res Clin Gastroenterol* 2004; **18**: 717–33.
9 Guo JP, Maurer AH, Fisher RS, Parkman HP. Extending gastric emptying scintigraphy from two to four hours detects more patients with gastroparesis. *Dig Dis Sci* 2001; **46**: 24–9.
10 Camilleri M, Malagelada JR, Brown ML, Becker G, Zinsmeister AR. Relation between antral motility and gastric emptying of solids and liquids in humans. *Am J Physiol* 1985; **245**: G580–5.
11 Collins PJ, Horowitz M, Chatterton BE. Proximal, distal and total stomach emptying of a digestible solid meal in normal subjects. *Br J Radiol* 1988; **61**: 12–8.
12 Urbain JL, Siegel JA, Charkes ND, Maurer AH, Malmud LS, Fisher RS. The two-component stomach: effects of meal particle size on fundal and antral emptying. *Eur J Nucl Med* 1989; **15**: 254–9.
13 Camilleri M, Zinsmeister AR, Greydanus MP, Brown ML, Proano M. Towards a less costly but accurate test of gastric emptying and small bowel transit. *Dig Dis Sci* 1991; **36**: 609.
14 Ziessman H, Bonta D, Goetze S, Ravich W. Experience with a simplified, standardized 4-hour gastric-emptying protocol. *J Nucl Med* 2007; **48**: 568–72.
15 Choi MG, Camilleri M, Burton DD *et al.* [13C]octanoic acid breath test for gastric emptying of solids: accuracy, reproducibility, and comparison with scintigraphy. *Gastroenterology* 1997; **112**: 1155–62.
16 Lee JS, Camilleri M, Zinsmeister AR *et al.* Toward office-based measurement of gastric emptying in symptomatic diabetics using [13C]octanoic acid breath test. *Am J Gastroenterol* 2000; **95**: 2751–61.
17 Corinaldesi R, Stanghellini V, Raiti C *et al.* Effect of chronic administration of cisapride on gastric emptying of a solid meal and on dyspeptic symptoms in patients with idiopathic gastroparesis. *Gut* 1987; **28**: 300–5.
18 Jiian R, Ducrot F, Ruskone A *et al.* Symptomatic, radionuclide and therapeutic assessment of chronic idiopathic dyspepsia. A double-blind placebo-controlled evaluation of cisapride. *Dig Dis Sci* 1989; **34**: 657–64.
19 Janssens J, Peeters TL, Vantrappen G *et al.* Improvement of gastric emptying in diabetic gastroparesis by erythromycin. Preliminary studies. *N Engl J Med* 1990; **322**: 1028–31.
20 Prather CM, Camilleri M, Thomforde GM, Forstrom LA, Zinsmeister AR. Gastric axial forces in experimentally delayed and accelerated gastric emptying. *Am J Physiol* 1993; **264**: G928–34.
21 Parkman HP, Gonlachanvit S, Hsu C-W *et al.* Effect of altering gastric emptying on postprandial glucose following a physiologic meal in type II diabetic patients. *Dig Dis Sci* 2003; **48**: 488–97.
22 Camilleri M. Diabetic gastroparesis. *N Engl J Med* 2007; **356**: 820–9.
23 Horowitz M, Harding P, Chatterton B, Collins P, Shearman D. Acute and chronic effects of domperidone on gastric emptying in diabetic autonomic neuropathy. *Dig Dis Sci* 1985; **30**: 1–9.
24 Tack J, Bisschops R, Sarnelli G. Pathophysiology and treatment of functional dyspepsia. *Gastroenterology* 2004; **127**: 1239–55.
25 Bredenoord AJ, Chial HJ, Camilleri M, Mullan BP, Murray JA. Gastric accommodation and emptying in evaluation of patients with upper gastrointestinal symptoms. *Clin Gastroenterol Hepatol* 2003; **1**: 264–72.
26 Kuo B, McCallum RW, Koch KL *et al.* Comparison of gastric emptying of a nondigestible capsule to a radiolabelled meal in healthy and gastroparetic subjects. *Aliment Pharmacol Ther* 2008; **27**: 186–96.
27 Rao SS, Kuo B, McCallum RW *et al.* Investigation of Colonic and Whole Gut Transit with Wireless Motility Capsule and Radioopaque Markers in Constipation. *Clin Gastroenterol Hepatol* 2009; **7**: 537–44.
28 Sarosiek I, Selover KH, Katz LA *et al.* The assessment of regional gut transit times in healthy controls and patients with gastroparesis using wireless motility technology. *Aliment Pharmacol Ther* 2010; **31**: 313–22.
29 Cassilly D, Kantor S, Knight LC *et al.* Gastric emptying of a non-digestible solid: assessment with simultaneous SmartPill pH and pressure capsule, antroduodenal manometry, gastric emptying scintigraphy. *Neurogastroenterol Motil* 2008; **20**: 311–9.
30 Mreyoud A, Rozov I, Moore J *et al.* Assessment of drug effects on gastric emptying and contractility using wireless capsule manometry. *Gastroenterology* 2009; **136**(Suppl 1): T1271.

31 Hasler WL, Saad RJ, Rao SS *et al.* Heightened colon motor activity measured by a wireless capsule in patients with constipation: relation to colon transit and IBS. *Am J Physiol Gastrointest Liver Physiol* 2009; **297**: G1107–14.

32 Kloetzer L, Chey WD, McCallum RW *et al.* Motility of the antroduodenum in healthy and gastroparetics characterized by wireless motility capsule. *Neurogastroenterol Motil* 2010; **22**: 527–33, e117.

33 Ghoos YF, Maes BD, Geypens BJ *et al.* Measurement of gastric emptying rate of solids by means of a carbon labeled octanoic acid breath test. *Gastroenterology* 1994; **104**: 1640–7.

34 Szarka LA, Camilleri M, Vella A *et al.* A stable isotope breath test with a standard meal for abnormal gastric emptying of solids in the clinic and in research. *Clin Gastroenterol Hepatol* 2008; **6**: 635–43.

35 *[C13]-Spirulina platensis Gastric Emptying Breath Test (GEBT): Investigator Brochure*. Brentwood, TN: Advanced Breath Diagnostics, LLC, 2005.

36 Schadewaldt P, Schommartz B, Wienrich G *et al.* Application of isotope-selective nondispersive infrared spectrometry (IRIS) for evaluation of [13C]octanoic acid gastric-emptying breath tests: comparison with isotope ratio-mass spectrometry (IRMS). *Clin Chem* 1997; **43**: 518–22.

37 Viramontes BE, Kim D-Y, Camilleri M *et al.* Validation of a stable isotope gastric emptying test for normal, accelerated or delayed gastric emptying. *Neurogastroenterol Motil* 2001; **13**: 567–74.

38 Sanaka M, Urita Y, Sugimoto M, Yamamoto T, Kuyama Y. Comparison between gastric scintigraphy and the [13C]-acetate breath test with Wagner–Nelson analysis in humans. *Clin Exp Pharmacol Physiol* 2006; **33**: 1239–43.

39 Odunsi ST, Camilleri M, Szarka LA, Zinsmeister AR. Optimizing analysis of stable isotope breath tests to estimate gastric emptying of solids. *Neurogastroenterol Motil* 2009; **21**: 706–e387.

40 Choi MG, Camilleri M, Burton DD *et al.* Reproducibility and simplification of 13C-octanoic acid breath test for gastric emptying of solids. *Am J Gastroenterol* 1998; **93**: 92–8.

41 Vella A, Lee JS, Camilleri M *et al.* Effects of pramlintide, an amylin analogue, on gastric emptying in type 1 and 2 diabetes mellitus. *Neurogastroenterol Motil* 2002; **14**: 123–31.

42 Keller J, Andresen V, Wolter J, Layer P, Camilleri M. Influence of clinical parameters on the results of 13C-octanoic acid breath tests: examination of different mathematical models in a large patient cohort. *Neurogastroenterol Motil* 2009; **21**: 1039–e83.

43 van de Casteele M, Luypaerts A, Geypens B *et al.* Oxidative breakdown of octanoic acid is maintained in patients with cirrhosis despite advanced disease. *Neurogastroenterol Motil* 2003; **15**: 113–20.

44 Jones KL, O'Donovan D, Horowitz M *et al.* Effects of posture on gastric emptying, transpyloric flow, and hunger after a glucose drink in healthy humans. *Dig Dis Sci* 2006; **51**: 1331–8.

45 Gentilcore D, Hausken T, Horowitz M, Jones KL. Measurements of gastric emptying of low- and high-nutrient liquids using 3D ultrasonography and scintigraphy in healthy subjects. *Neurogastroenterol Motil* 2006; **18**: 1062–8.

46 Fidler J, Bharucha AE, Camilleri M *et al.* Application of magnetic resonance imaging to measure fasting and postprandial volumes in humans. *Neurogastroenterol Motil* 2009; **21**: 42–51.

47 Simren M, Stotzer PO. Use and abuse of hydrogen breath tests. *Gut* 2006; **55**: 297–303.

48 La Brooy SJ, Male PJ, Beavis AK, Misiewicz JJ. Assessment of the reproducibility of the lactulose H_2 breath test as a measure of mouth to cecum transit time. *Gut* 1983; **24**: 893–6.

49 Miller MA, Parkman HP, Urbain JL *et al.* Comparison of scintigraphy and lactulose breath hydrogen test for assessment of orocecal transit: lactulose accelerates small bowel transit. *Dig Dis Sci* 1997; **42**: 10–8.

50 Geypens B, Bennink R, Peeters M *et al.* Validation of the lactose-[13C]ureide breath test for determination of orocecal transit time by scintigraphy. *J Nucl Med* 1999; **40**: 1451–5.

51 Morrison DJ, Dodson B, Preston T, Weaver LT. Gastrointestinal handling of glycosyl [13C]ureides. *Eur J Clin Nutr* 2003; **57**: 1017–24.

52 Krevsky B, Maurer AH, Niewiarowski T, Cohen S. Effect of verapamil on human intestinal transit. *Dig Dis Sci* 1992; **37**: 919–24.

53 Charles F, Camilleri M, Phillips SF, Thomforde GM, Forstrom LA. Scintigraphy of the whole gut: clinical evaluation of transit disorders. *Mayo Clin Proc* 1995; **70**: 113–8.

54 Argenyi EE, Soffer EE, Madsen MT, Berbaum KS, Walkner WO. Scintigraphic evaluation of small bowel transit in healthy subjects: inter- and intrasubject variability. *Am J Gastroenterol* 1995; **90**: 938–42.

55 Camilleri M, Hasler WL, Parkman HP, Quigley EM, Soffer E. Measurement of gastrointestinal motility in the GI laboratory. *Gastroenterology* 1998; **115**: 747–62.

56 Maurer AH, Krevsky B. Whole-gut transit scintigraphy in the evaluation of small-bowel and colonic transit disorders. *Semin Nucl Med* 1995; **25**: 326–38.

57 Grybäck P, Jacobsson H, Blomquist L, Schnell PO, Hellström PM. Scintigraphy of the small intestine: a simplified standard for study of transit with reference to normal values. *Eur J Nucl Med Mol Imaging* 2002; **29**: 39–4.

58 Bennink R, Peeters M, Van den Maegdenbergh V *et al.* Evaluation of small-bowel transit for solid and liquid test meal in healthy men and women. *Eur J Nucl Med* 1999; **26**: 1560–6.

59 Deiteren A, Camilleri M, Bharucha AE *et al.* Performance characteristics of scintigraphic colon transit measurement in health and irritable bowel syndrome and relationship to bowel functions. *Neurogastroenterol Motil* 2010; **22**: 415–23, e95.

60 Camilleri M, Brown ML, Malagelada JR. Impaired transit of chyme in chronic intestinal pseudoobstruction. Correction by cisapride. *Gastroenterology* 1986; **91**: 619–26.

61 Camilleri M, Malagelada JR, Abell TL *et al.* Effect of six weeks of treatment with cisapride in gastroparesis and intestinal pseudoobstruction. *Gastroenterology* 1989; **96**: 704–12.

62 Prather CM, Camilleri M, Zinsmeister AR, McKinzie S, Thomforde G. Tegaserod accelerates orocecal transit in patients with constipation-predominant irritable bowel syndrome. *Gastroenterology* 2000; **118**: 463–8.

63 Balan K, Alwis L, Sonoda LI *et al.* Utility of whole gut transit scintigraphy in patients with chronic gas-

trointestinal symptoms. *Nucl Med Commun* 2010; **31**: 328–33.
64 Camilleri M, Thorne NK, Ringel Y *et al.* Wireless pH-motility capsule for colonic transit: prospective comparison with radiopaque markers in chronic constipation. *Neurogastroenterol Motil* 2010; **22**: 874–82.
65 Connell AM, McCall J, Misiewicz JJ, Rowlands EN. Observations on the clinical use of radio pills. *Br Med J* 1963; **2**: 771–4.
66 Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ, Hardcastle JD. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. *Gut* 1988; **29**: 1035–41.
67 Zarate N, Mohammed S, O'Shaughnessy E *et al.* Accurate localisation of a fall in pH within the ileo-caecal region. *Neurogastroenterol Motil* 2009; **21**(Suppl 1): 43. (abstract).
68 Sarosiek I, Sarosiek J, Rao S *et al.* Comparisons of alimentary tract transit times among normal subjects from two multicentre trials using SmartPill wireless pH/pressure recording capsule: its clinical implications. *Am J Gastroenterol* 2007; **102**(Suppl 2): S170.
69 Rao SS, Mysore KR, Attaluri A, Valestin J. Diagnostic utility of wireless motility capsule in gastrointestinal dysmotility. *J Clin Gastroenterol* 2011. (in press).
70 De Iorio F, Malagelada C, Azpiroz F *et al.* Intestinal motor activity, endoluminal motion and transit. *Neurogastroenterol Motil* 2009; **21**: 1264–71.
71 Stathopoulos E, Schlageter V, Meyrat B, Ribaupierre Y, Kucera P. Magnetic pill tracking: a novel non-invasive tool for investigation of human digestive motility. *Neurogastroenterol Motil* 2005; **17**: 148–54.
72 Hinton JM, Lennard-Jones JE, Young AC. A new method for studying gut transit times using radioopaque markers. *Gut* 1969; **10**: 842–7.
73 Abrahamsson H, Antov S, Bosaeus I. Gastrointestinal and colonic segmental transit time evaluated by a single abdominal x-ray in healthy subjects and constipated patients. *Scand J Gastroenterol* 1988; **152**: 72–80.
74 Chaussade S, Khyari A, Roche H *et al.* Determination of total and segmental colonic transit time in constipated patients Results in 91 patients with a new simplified method. *Dig Dis Sci* 1989; **34**: 1168–72.
75 Metcalf AM, Phillips SF, Zinsmeister AR *et al.* Simplified assessment of segmental colonic transit. *Gastroenterology* 1987; **92**: 40–7.
76 Sadik R, Abrahamsson H, Stotzer PO. Gender differences in gut transit shown with a newly developed radiological procedure. *Scand J Gastroenterol* 2003; **38**: 36–42.
77 Southwell BR, Clarke MC, Sutcliffe J, Hutson JM. Colonic transit studies: normal values for adults and children with comparison of radiological and scintigraphic methods. *Pediatr Surg Int* 2009; **25**: 559–72.
78 Pomerri F, Frigo AC, Grigoletto F *et al.* Error count of radiopaque markers in colonic segmental transit time study. *Am J Roentgenol* 2007; **189**: W56–9.
79 van der Sijp JR, Kamm MA, Nightingale JM *et al.* Radioisotope determination of regional colonic transit in severe constipation: comparison with radio opaque markers. *Gut* 1993; **34**: 402–8.
80 Corazziari E, Badiali D, Habib FI *et al.* Small volume isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in treatment of chronic nonorganic constipation. *Dig Dis Sci* 1996; **41**: 1636–42.
81 Harish K, Hazeena K, Thomas V *et al.* Effect of tegaserod on colonic transit time in male patients with constipation-predominant irritable bowel syndrome. *J Gastroenterol Hepatol* 2007; **22**: 1183–9.
82 Sloots CE, Poen AC, Kerstens R *et al.* Effects of prucalopride on colonic transit, anorectal function and bowel habits in patients with chronic constipation. *Aliment Pharmacol Ther* 2002; **16**: 759–67.
83 Rao SSC, Mudipalli RS, Stessman M *et al.* Investigation of the utility of colorectal function tests and Rome II criteria in dyssynergic defecation (Anismus). *Neurogastroenterol Motil* 2004; **16**: 1–8.
84 Sadik R, Abrahamsson H, Ung KA, Stotzer PO. Accelerated regional bowel transit and overweight shown in idiopathic bile acid malabsorption. *Am J Gastroenterol* 2004; **99**: 711–8.
85 Camilleri M. Scintigraphic biomarkers for colonic dysmotility. *Clin Pharmacol Ther* 2010; **87**: 748–53.
86 Proano M, Camilleri M, Phillips SF *et al.* Transit of solids through the human colon: regional quantification in the unprepared bowel. *Am J Physiol* 1990; **258**: G856.
87 Camilleri M, Zinsmeister AR. Towards a relatively inexpensive, noninvasive, accurate test for colonic motility disorders. *Gastroenterology* 1992; **103**: 36.
88 Lundin E, Graf W, Garske U, Nilsson S, Maripuu E, Karlbom U. Segmental colonic transit studies: comparison of a radiological and a scintigraphic method. *Colorectal Dis* 2007; **9**: 344–51.
89 Cremonini F, Mullan BP, Camilleri M *et al.* Performance characteristics of scintigraphic transit measurements for studies of experimental therapies. *Aliment Pharmacol Ther* 2002; **16**: 1781–90.
90 Manabe N, Wong BS, Camilleri M *et al.* Lower functional gastrointestinal disorders: evidence of abnormal colonic transit in a 287 patient cohort. *Neurogastroenterol Motil* 2010; **22**: 293–e82.
91 Stivland T, Camilleri M, Vassallo M *et al.* Scintigraphic measurement of regional gut transit in idiopathic constipation. *Gastroenterology* 1991; **101**: 107–15.
92 Verne GN, Hocking MP, Davis RH *et al.* Long-term response to subtotal colectomy in colonic inertia. *J Gastrointest Surg* 2002; **6**: 738–44.
93 Maqbool S, Parkman HP, Friedenberg FK. Wireless capsule motility: comparison of the SmartPill® GI monitoring system with scintigraphy for measuring whole gut transit *Dig Dis Sci* 2009; **54**: 2167–74.
94 Rao S, Valestin J, Attaluri A, Wilding G, Semler JR. Inter-observer agreement for regional and whole gut transit measurement by wireless motility capsule in health, gastroparesis and constipation. *Am J Gastroenterol* 2010; **105**: 1161.
95 Ringel Y, Gelfond D, Galanko JA *et al.* Alterations in intestinal transit in subgroups of patients with functional bowel disorders and healthy controls – a wireless motility capsule study. *Am J Gastroenterol* 2010; **105**: 1159.
96 Saad R, Rao SS, Koch KL *et al.* Do stool form and frequency correlate with whole gut and colonic transit? Results from a multicenter study in constipated individuals and healthy controls *Am J Gastroenterol* 2010; **105**: 403–11.
97 Lee A, Michalek W, Wiener SM, Kuo B. Clinical impact of a wireless motility capsule – a retrospective review. *Gastroenterology* 2010; **138**: T1067.