REVIEWS

Rome III: New Standard for Functional Gastrointestinal Disorders

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Abstract

The publication in the April, 2006 issue of Gastroenterology of Rome III has made available to the scientific world an enhanced and updated version of the Rome criteria and related information on the functional GI disorders. It is expected that the criteria will be adopted and used by physicians, pharmaceuticals and regulatory agencies worldwide, just as the previous Rome II became the standard for clinical practice and research. In this issue of J Gastrointestin Liver Dis, these Guidelines, the Rome III, are presented. Also included are some of the differences between Rome II and Rome III criteria as well as the rationale for publishing this new version.

Key words

Functional gastrointestinal disorders - Rome III

Introduction

Functional gastrointestinal disorders (FGID) represent a common and important class of disorders within gastroenterology. The large number of patients suffering from the FGIDs, as well as the high frequency of functional GI symptoms in general within the population, the health care burden produced by the use of medical services and medications for these conditions, and its eventual outcome in terms of work absenteeism are well known (1-4).

Quite possibly, increased awareness of the FGIDs may have resulted from the activity of the Rome working group, later called the Rome Foundation. This group introduced a standard for the classification and diagnosis of the FGID, the *Rome criteria*. A series of documents in the early 1990's published in Gastroenterology International was eventually compiled into a book that was published in 1994 (5). The criteria were then updated as Rome II in 2000 (6) and published in abbreviated form as a supplement of Gut, 1999.

J Gastrointestin Liver Dis
September 2006 Vol.15 No.3, 237-241
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The need for a new version of Rome criteria

In recent years the interest in the FGIDs by gastroenterologists, internists, psychologists and family physicians as well as attention by the general has grown considerably. This could be attributed to increased attention to these disorders by the media, pharmaceutical companies, academic and interest organizations like the International Foundation for Functional Gastrointestinal Disorders and the Functional Brain Gut Research Group of the American Gastroenterological Association. But what has led to the development of another set of criteria: Rome III has several explanations.

The availability of new data from scientific progress

The number of studies and publications on the FGID increased along with the progress of newer investigative methods. In Fig 1 is presented the dynamics of the publications on irritable bowel syndrome (IBS), a major FGID, indexed on Medline. These studies served to legitimize these conditions in a positive way, not just by exclusion of other disorders. The assessment of motility has improved (7-9). The wider use of the barostat, as the main technique for assessing visceral hypersensitivity has provided evidence for the role of visceral sensitivity in understanding these conditions (10). Finally, another novel area of development has been the progress in brain imaging: positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). These modalities offer a window into the central modulation of GI function and its linkages to emotional and cognitive areas (11). Thus the nature of FGID as disorders of brain-gut interactions is now

eminently amenable to scientific study. The psychological instruments permitting the categorization and quantification of emotions, stress, and cognitions have also been better standardized (12), and these measures help us determine the role of psychosocial factors on symptom generation and health outcomes. Finally, the molecular investigation of brain and gut peptides, mucosal immunology, inflammation, and alterations in the bacterial flora of the gut provide the translational basis for GI symptom generation.

The advent of new drugs and the necessity to develop new therapies

There is a growing competition in the marketplace to synthesize and produce new medications to meet the demands of patients now identified with FGIDs. In recent years we have witnessed the development and release of new pharmacological agents to treat altered motility, visceral hypersensitivity, and stress-mediated effects in patients with FGID. The newer agents include the 5-HT agonists and antagonists and several other gut receptor active agents for constipation and diarrhea, centrally acting agents including antidepressants to treat stress-mediated effects of CNS modulation of the gut (13-15). In addition, different forms of psychotherapy have shown their benefit in treating the FGID (16-17).

The shift of paradigm in medical conceptualization

The basic paradigm of the modern medicine has traditionally relied on the concepts promoted by Descartes of biological reductionism and dualism, which in medicine, seeks to find a single biological etiology for every clinical condition (18). In the last decades we have moved away from this reductionistic model of disease to a more holistic paradigm of the biopsychosocial model of disease. Here, illness (the person's experience of ill health), and disease (objective histopathological findings) are viewed as equally important in understanding the clinical expression of a medical condition, and this refuted the traditional reductionistic model of disease. The reductionistic disease-based biomedical model harmonized with Descartes' separation of mind and body at the time when society was accepting the concept of separation of church and state (19). What resulted was permission to dissect the human body (which was previously forbidden), so disease was defined by what was seen (i.e., pathology based on abnormal morphology). This approach led to centuries of valuable research producing appropriated treatments for many diseases. However, the concept of the mind (i.e., the central nervous system, CNS) as being amenable to scientific study or as playing a role in illness and disease was marginalized: the mind was considered the seat of the soul, and was not to be tampered with. More recent scientific studies link the mind and body as part of a system where their dysregulation can produce illness and disease. By embracing this integrated understanding, the biopsychosocial model allows for symptoms to be both physiologically multidetermined and modifiable by socio-cultural and psychosocial influences (20, 21).

The application of this model of Engel to the FGIDs helps to explain how changes in early life, genetic factors and environmental factors, may affect the psychosocial development (susceptibility to life stress, psychological state, coping skills, social support) and/or the development of gut dysfunction (i.e., abnormal motility, visceral hypersensitivity, inflammation, or altered bacterial flora), all of which lead to the clinical expression of the disorder. Furthermore, these brain-gut variables mutually interact to influence their expression. Therefore the FGID are the clinical product of the interaction of psychosocial factors and altered

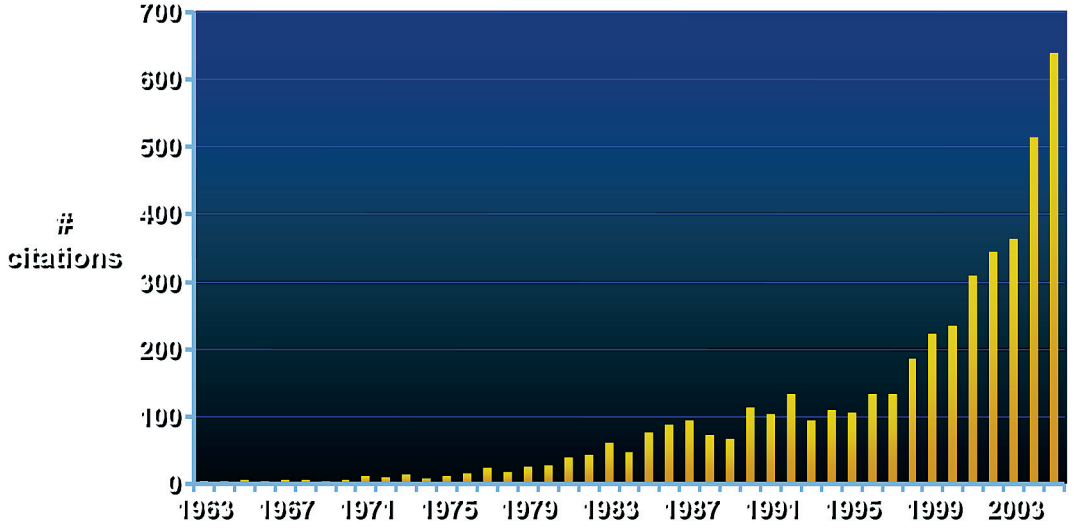

Fig.1 Number of Medline indexed journal papers on IBS.

gut physiology via the brain-gut axis (22). For example, an individual with a bacterial gastroenteritis or other bowel disorder who has no concurrent psychosocial difficulties and good coping skills may not develop the clinical syndrome (or be aware of it) or, if it does develop, may not perceive the need to seek medical care. Another individual with coexistent psychosocial comorbidities, high life stress, abuse history, or maladaptive coping, may develop a FGID and visit more frequently the physician and have a worse clinical outcome.

From Rome II to Rome III

A great deal of progress in the field has evolved from the beginning of the Rome process in 1989 (23). The publications of the Rome criteria in journals and books are presented in chronological order in Fig.2. All physicians now recognize the FGIDs as true clinical entities. Researchers and clinicians worldwide are more involved with these disorders, and the Rome process has played an important role in categorizing and disseminating the new and evolving knowledge. These disorders are now a prominent part of undergraduate and postgraduate medical curricula, clinical training programs, and international symposia. The number of papers in the FGIDs in peer-reviewed journals has increased dramatically. In a parallel fashion these disorders are commonly reported in newspapers, television and even cinema. But now there are future challenges to be faced: a need for an improved understanding of the relationships between mind and gut, and the translation of basic neurotransmitter function into clinical symptoms and their impact on the patient's health status and quality of life. There is also a need to educate clinicians and the general public on this rapidly growing knowledge and, in the process, continue to legitimize these disorders to society (12).

The Rome process for developing these criteria is a rigorous one. The consensus process was initiated by Professor Aldo Torsoli at the International Congress of Gastroenterology in Rome (Roma 1989). He charged working team committees to use a "Delphi" method of decision-making, which fosters a team to produce consistency in opinion, or consensus (although not necessarily total agreement) for difficult questions not easily addressed. The Roma '88 meeting led to the first presentation of criteria for IBS, which later evolved into a classification system for all the functional GI disorders (1) eventually evolving into the Rome criteria (Rome I) [reference Rome I book). Later, the Rome II committees and more recently the Rome III board took on the responsibility to enhance these activities using a rigorous 4-year, multiple step process.

What is preserved in Rome III?

The Rome III classification has been printed in this issue of *J Gastrointestin Liver Dis* in the section Guidelines.

It maintains the principle of symptom-based diagnostic criteria like the DSM classification for mental disorders. The classification relies on the organs where the symptoms presumably are produced. They are in order from esophagus to anus. This classification is maintained in the pediatric child/adolescent classification system, though is based more on developmental stages for the pediatric neonate/toddler system.

The FGIDs include 6 major domains for adults: esophageal (category A), gastroduodenal (category B), bowel (category C), functional abdominal pain syndrome (category D), biliary (category E), and anorectal (category F).

Each category site contains several disorders, each having relatively specific clinical features. So, the functional bowel disorders (category C) include IBS (C1), functional bloating (C2), functional constipation (C3) and functional

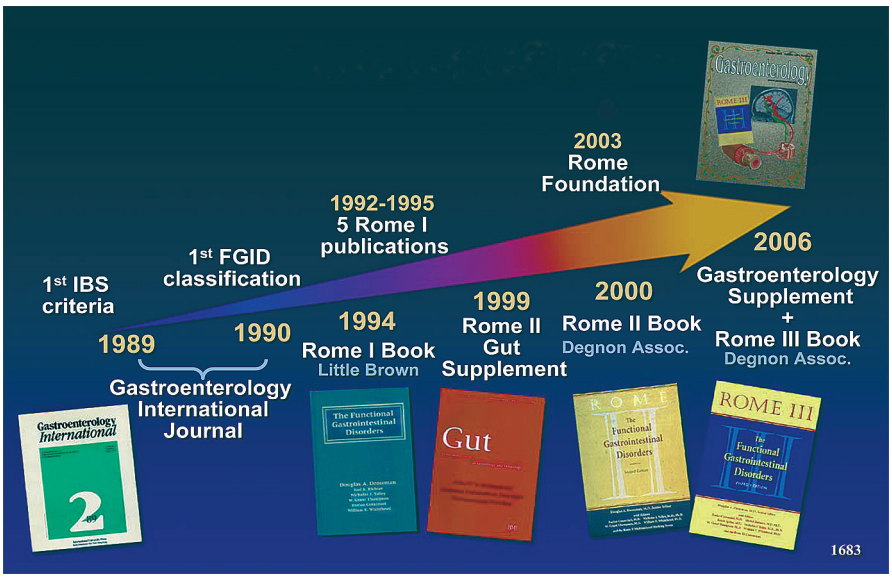

Fig.2 Chronology of the Rome criteria publications.

diarrhea (C4), which anatomically are attributed to the small bowel, colon, and rectum. Thus, while symptoms (e.g., diarrhea, constipation, bloating, pain) may overlap across these disorders, IBS (C1) is more specifically defined as pain associated with change in bowel habit, and this is distinct from functional diarrhea (C4), characterized by loose stools and no pain, or functional bloating (C2), where there is no change in bowel habit. Each condition also has different diagnostic and treatment approaches.

The symptoms of the FGIDs are derived from combinations of their physiological determinants: increased motor reactivity, enhanced visceral hypersensitivity, altered mucosal immune and inflammatory function (which includes changes in bacterial flora), and altered CNS-enteric nervous system (ENS) regulation (as influenced by psychosocial and sociocultural factors and exposures). For example, fecal incontinence (category F1) may primarily be a disorder of motor function, while functional abdominal pain syndrome (category D) is primarily understood as amplified central perception of normal visceral input. IBS (category C1) is more complex, and results from a combination of dysmotility, visceral hypersensitivity, mucosal immune dysregulation, alterations of bacterial flora, and CNS-ENS dysregulation. The contribution of these factors may vary across different individuals or within the same individual over time. Thus, the clinical value of separating the functional GI symptoms into discrete conditions is that they can be reliably diagnosed and better treated (12). The Rome III classification system is based on the premise that for each disorder there are symptom clusters that "breed true" across clinical and population groups. This presumption provides a framework for identification of patients for research that is modified as new scientific data emerges.

The rationale for classifying the functional GI disorders into symptom-based subgroups are based on the site-specific differences between symptoms, i.e., the fact that symptoms result from multiple influences, from epidemiologic data showing similar frequencies of these disorders across cultures, and finally, out of the need for diagnostic standards in order to conduct clinical care and research.

There are several limitations and qualifications to the use of symptom-based criteria:

- Other diseases may coexist and have to be excluded, and symptoms may overlap with other FGID. It is common for functional GI disorders to coexist, and the criteria permit the coexistence of more than one FGID. Examples would be esophageal chest pain (A2) or globus (A4), with IBS (C1) or fecal incontinence (F1). However, there are situations where a hierarchical classification of the FGIDs is required. For example, when criteria for both IBS (C1) and epigastric pain syndrome (B1b) are fulfilled, the diagnosis of IBS only is made when the epigastric pain is relieved by defecation. Similarly functional bloating (C2) exists only when IBS and the dyspeptic conditions are excluded, since bloating is common to both these other conditions, and a diagnosis of functional constipation (C3) is made only if IBS criteria are not met.

- Diagnostic categories do not include psychosocial criteria.

- The proposed diagnostic criteria were originated by the consensus of experts in the field and have since been modified only if there is compelling evidence to do so.

- All changes in criteria relate to a rationale that is provided in corresponding chapter of the Rome III book chapter. In some cases, recommendations for changes (e.g., dyspeptic criteria, subtypes of IBS) are not yet proven but are supported by compelling evidence.

- New criteria will be tested in future studies now underway, and this will form the basis for future modifications of the criteria.

What has changed in Rome III?

The changes from Rome II to Rome III reflect mainly updates in the literature and committee recommendations derived from these new data. In addition, a few modifications in the categories and criteria were made. These are:

1. Change of chronological criteria. Symptoms are now recommended to originate 6 months prior to diagnosis and be currently active (i.e., meet criteria) for 3 months. This time frame is less restrictive when compared to Rome II (12 weeks of symptoms over 12 months) and is easier to understand and apply in research and clinical practice.

2. Changes in classification categories:

a. Rumination syndrome moved from functional esophageal (Category A) to functional gastroduodenal disorders (Category B). This reflects the evidence that this disorder originates from disturbances in the stomach and abdomen.

b. Removal of functional abdominal pain syndrome (FAPS) from functional bowel disorders (Category C) into its own category (Category D). This is based on growing evidence that FAPS relates more to CNS amplification of normal regulatory visceral signals rather than functional abnormalities within the GI tract.

3. Creation of two pediatric categories. The Rome II category of Childhood Functional GI Disorders (called Category G) has been split into two categories. The pediatric FGID are now classified as Childhood Functional GI Disorders: Neonate/Toddler (Category G) and Childhood Functional GI Disorders: Child/Adolescent (Category H). This is due to the different clinical conditions that arise between these two categories relating to growth and development of the child.

4. Criteria changes:

a. Functional Dyspepsia. For Rome III, functional dyspepsia is de-emphasized as an entity for research due to the heterogeneity of this symptom complex as defined. Instead, the committees recommend two conditions that are subsumed under the functional dyspepsia "umbrella": (a) Postprandial distress syndrome, and (b) Epigastric pain

syndrome. These are similar to dysmotility-like and ulcer-like dyspepsia of Rome II. However, they are now defined by a complex of symptom features with physiological support rather than being based on the predominant symptom of epigastric discomfort or pain respectively.

b. More restrictive criteria for functional disorders of the gallbladder and sphincter of Oddi. There are more defining features and exclusions required for symptom-based diagnosis of these conditions. In doing so, we have reduced the patient population who would then receive invasive studies like endoscopic retrograde cholangiopancreatography (ERCP) and manometry to confirm the diagnosis and be treated.

c. Revision of IBS subtypes criteria. The committees are recommending that diarrhea, constipation and mixed subtypes be based on a simple classification related to stool consistency. However, the bowel sub-typing used in Rome II for diarrhea-predominant IBS (IBS-D) and constipation-predominant IBS (IBS-C) is still acceptable.

Conclusion

It is expected that the new Rome III criteria will rapidly gain acceptance and use as occurred with Rome II, and become the new standard for diagnosis and care of the FGIDs. Of course, papers and studies with Rome II criteria will continue to be issued. There is a need to validate the new terms in non-Anglo-Saxon languages like the Latin languages, especially the postprandial distress syndrome.

The members of the Rome Foundation hope that the Rome criteria will enhance the development of our knowledge on the FGID.

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