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REVIEW

Diagnosis of inflammatory bowel disease: Potential role of molecular biometrics

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Abstract

Accurate diagnosis of predominantly colonic inflammatory bowel disease (IBD) is not possible in 30% of patients. For decades, scientists have worked to find a solution to improve diagnostic accuracy for IBD, encompassing Crohn's colitis and ulcerative colitis. Evaluating protein patterns in surgical pathology colectomy specimens of colonic mucosal and submucosal compartments, individually, has potential for diagnostic medicine by identifying integrally independent, phenotype-specific cellular and molecular characteristics. Mass spectrometry (MS) and imaging (I) MS are analytical technologies that directly measure molecular species in clinical specimens, contributing to the in-depth understanding of biological molecules. The biometric-system complexity and functional diversity is well suited to proteomic and diagnostic studies. The direct analysis of cells and tissues by Matrix-Assisted-Laser Desorption/Ionization (MALDI) MS/IMS has relevant medical diagnostic potential. MALDI-MS/IMS detection generates molecular signatures obtained from specific cell types within tissue sections. Herein discussed is a perspective on the use of MALDI-MS/IMS and bioinformatics technologies for detection of molecular-biometric patterns and identification of differentiating proteins. I also discuss a perspective on the global challenge of transferring technologies to clinical laboratories dealing with IBD issues. The significance of serologic-immunometric advances is also discussed.

Key words: Inflammatory bowel disease; Diagnosis; Advances and challenges; MALDI-MS/IMS; Molecular biometrics; Immunometrics

Core tip: Pouch surgery (the restorative proctocolectomy and ileal pouch-anal anastomosis for the curative surgical treatment of ulcerative colitis and familial adenomatous polyposis) replaces the colon and rectum after proctocolectomy with a pouch constructed from the distal small bowel (ileum) and sutured to the anal canal above the dentate/pectinate line preserving the anal sphincters. The operation restores gut continuity, defecation, deferral, and discrimination, if the diagnosis is correct, which is unpredictable in 30% of the colonic-inflammatory bowel disease-patients. Mass spectrometry and imaging mass spectrometry are groundbreaking, non-invasive analytical technologies with the ability to directly measure individual molecular species in complex clinical specimens. These technologies provide quantitative and qualitative analysis of cellular systems, and allow differentiation between disease and normal molecules from the same organ. These characteristics offer diagnostic and prognostic value for clinical medicine.

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INTRODUCTION

Inflammatory bowel disease

Colonic inflammatory bowel disease (IBD) comprises Crohn's colitis (CC) and ulcerative colitis (UC), a group of diseases of the gastrointestinal (GI) tract characterized by chronic relapsing and remitting inflammation[1,2]. IBD affects as many as 1.6 million persons in the United States and 2.2 million in Europe. The incidence is increasing worldwide[1-5]. In spite of advances in IBD-therapy, IBD hospitalizations and surgery rates in the United States have increased significantly since 1990[6]. IBD is one of the five most prevalent GI disease burdens in the United States, with annual overall health care costs of more than $1.7 billion[7,8]. One to two of every 1000 people in developed countries are affected with IBD[9], and global rates seem to be increasing[1,10-12], attributable to the rapid modernization and Westernization of the population[1]. These chronic diseases result in significant morbidity and mortality, compromising quality of life and life expectancies. While there is no drug for cure for these diseases, the last three decades have seen major advances in the molecular understanding intestinal immune responses and how they relate to IBD. This, in turn, has led to the development and refinement of several new treatments. Most significant has been the development of restorative proctocolectomy (RPC) with ileal pouch-anal anastomosis (IPAA). The pelvic pouch surgery allows for the removal of the entire colon while maintaining transanal fecal continence without a permanent diverting loop ileostomy. The success of RPC (judged by the entire removal of a diseased colon while preserving gastrointestinal continuity, bowel evacuation, continence and fertility) restores physiological function and greatly improves patient health quality of life. Successful RPC also frees the healthcare system from the immense burden of current lifelong, non-curative treatments. These outcomes are dependent on a correct diagnosis and meticulous surgical techniques available at well-established IBD centers[13-15].

The etiology of IBD poorly understood. The general consensus holds that IBD is an automatic dysfunction triangle of antigen and antibody reaction against mucosal response to commensal bacteria. The fundamental question is why the immune system responds aggressively to harmless, ever-present bacteria, releasing complex mixes of cytokines, chemokines and other substances that cause inflammation. One possible explanation is that the gut immune system is compromised because of defects in the barrier function of the gut luminal epithelium[16]. Although the etiology of IBD is at present not delineated, histopathologic and clinical assessments demonstrate that CD and UC, the two major classifications of IBD, are indeed distinct entities and have different causes and discrete mechanisms of tissue damage and treatment[16-21]. UC results in inflammation and ulcerations in the mucosal and to a lesser degree submucosal linings of the colon and rectum. CD differs in that it may result in inflammation deeper within the intestinal wall (transmullary) and can occur in any parts of the digestive system (including the mouth, esophagus, stomach, duodenum, small intestine, colon and rectum). Further, Crohn's may also involve other organs outside the GI system through fistulization[22,23]. Crohn's is diagnosed in at least four patients per 100000 in the United States, and the incidence and prevalence is rising worldwide[1,10-12].

Diagnosis challenges in IBD

The current standard of care for IBD treatment is based on steroids and immunosuppressant agents, including glucocorticoids, aminosalicylates, cyclosporine, methotrexate and biologic agents such as anti-TNF-α and IL1-β. The correct IBD diagnosis is crucial for providing correct, evidence-based treatment, since treatment response and complications differ significantly among UC and CC patients[24]. The absence of specific phenotypes indicating the particular disease condition challenges pathologist interpretation and categorization of tissue morphology, subsequently leading to difficulties in diagnosis and consistent standard of care[25]. However, despite advances in our understanding of the genetic[16,26], immunologic[26,27], and environmental[1,24,28] influences that may trigger complex IBD pathologies, to date there is no single indicator sensitive enough to accurately and consistently delineate CC and UC. The available data indicate that genetic factors determine an individual's susceptibility to developing IBD, and environmental factors elicit cellular responses that drive disease progression. Histological evaluation and interpretation of tissue provides insights that directly impact care[25]. Pathologists rely mainly on microscopic visual inspection and interpretation of stained and/or dyed tissue sections to identify the disease state of a patient sample[29,30]. Inherently, these procedures possess a significant degree of subjectivity[31] and are fraught with problems[31,32]. Rigorous training in pathology subspecialties has attempted to improve the standard of care and avoid unnecessary mistakes[33]. Despite these extremely thorough standards, inevitable situations arise in which objectivity cannot be guaranteed and where significant disagreement occurs between specialists[34]. This challenge is common for IBD patient populations[13,15,35,36] To date, there is no single, absolute diagnostic test[37,38]. A diagnosis should neither be based on nor excluded by any one variable or result[39]. The consensus statement on the diagnosis, management and surveillance of both CC[40] and UC[41] recommend that "multiple" tissue biopsies from at list five sites around the colon and rectum should be collected for support of a reliable diagnosis. Of these six sites a minimum of two samples from each should be sampled[40,41]. Although the procedure is reliable, it is invasive and uncomfortable to the patients.

Table 1 Microscopic features used for the diagnosis of Crohn's colitis

Colon	
Architecture	
Crypt architectural irregularity	Focal
	Diffuse
Reduces crypt numbers/mucosal atrophy	
Irregular surface	
Chronic inflammation	
Distribution I	Focal increased in intensity
	Patchy increase
Distribution II	Diffuse increase
	Superficial
Granulomas	Transmucosal
Mucin granulomas	Basal plasma cells
Polymorph inflammation	
Lamina propria	Focal
Crypt epithelial polymorphs	Diffuse
Polymorph exudates	
Epithelial changes	
Erosion/ulceration	
Mucin	Depletion
	Preservation
Paneth cells distal to hepatic flexure	
Epithelial-associated changes	
Increased intraepithelial lymphocytes > 15	
Terminal ileum/Ileocecal /Cecum	
Architecture	Villus irregularity
	Crypt architecture
Epithelial changes	Irregularity
	Pseudopyloric gland
	Metaplasia

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Inaccurate diagnosis in IBD and consequences

When IBD predominantly involves the colon, differentiation between CC from UC is often challenging. Inaccurate diagnoses are estimated to occur in 30% of IBD patients[42,43]. In most cases the diagnostic uncertainty arises from the overlap of clinical and histologic features, making CC appear like UC[44]. This scenario is particularly relevant to young children, a population in which IBD consists of up to 80%. The differentiation between UC and CC relies on a compilation of clinical, radiologic, endoscopic, and histopathologic interpretations[40]; a compilation that is not always accurate. An estimated 15% of IBD patients are indistinguishable and are labeled as "indeterminate colitis" (IC)[45-47]. In addition, another 15% of the colonic IBD cases that undergo pouch surgery resulting from a definitive UC diagnosis (based on the pathologist's initial designation of endoscopic biopsies and colectomy specimen) will have their original UC diagnosis changed to CC based on the postoperative follow-up when clinical and histopathology changes indicate development of CC in the ileal pouch[15,35,36,48,49]. One-half of these patients will require pouch excision or diversion[49].

Because of the unpredictable nature of IBD, side effects of medications, and potential complications, some of which may end in sudden incapacitation, IBD is becoming a global health concern. Distinguishing between CC and UC is critical to therapy. The clinical experience suggests that identifying patients with CC and positive outcomes after pouch surgery is arduous. Thus, RPC should be contraindicated for CC patients, whereas IPAA is standard acceptable care for patients with UC and IC who are predicted likely to develop UC. Inevitably, pouch complications are significantly higher in patients with CC (± 64%) and IC (± 43%) *vs* patients having UC (± 22%) ($P < 0.05$)[46,47,49]. This diagnostic dilemma and the potential morbidity from a wrong diagnosis and unnecessary and/or inappropriate surgical interventions underscore the importance of research strategy focused at improving diagnosis of the colitides using molecular biometrics[42,50-52].

Clinico-histopathologic findings in Crohn's colitis

Crohn's colitis is recognized to encompass a heterogeneous group of disorders[38]. Usually CC is segmental with deep inflammation where the disease activity is transmural, with lymphoid composite extending to the sub-serosa. The Montreal classification[53] and the Paris pediatric modification[54] have brought consistency to definitions of subtypes of CC and of colitides. It is noteworthy that both the Montreal and Paris classifications rely on the location of gross disease, *i.e.*, visible lesions with more than a few aphthous ulcers. Patterns of macroscopic involvement, rather than microscopic, have been useful traditionally in predicting clinical course, as exemplified by the tendency of small bowel disease, particularly, to stricture over time. Despite the fact that microscopic involvement does not define subtypes of CC, the role of histology in the diagnosis of CC does differ according to the anatomic location of macroscopic disease[38].

Histologic features useful for the diagnosis of CC have been reviewed by Griffiths[38], (Table 1) but, according to Van Assche *et al*[40] presented at The second European evidence-based Consensus on the diagnosis and management of Crohn's colitis, there are no data available as to how many of these features must be present to allow a firm diagnosis[40]. Focal (discontinuous) chronic (lymphocytes and plasma cells) inflammation and patchy chronic inflammation, focal crypt irregularity (discontinuous crypt distortion) and granulomas (not related to crypt injury) are the generally accepted microscopic features which allow a diagnosis of CC[40]. Within one histologic section, inflammation may be immediately adjacent to an uninflamed microscopic "skip area". Mucosal changes may resemble ulcerative or infectious colitis with infiltration of the crypts by polymorphonuclear leukocytes (cryptitis or crypt abscesses), and distortion of crypt architecture. Granulomas (collections of monocytes/macrophages) in the lamina propria (not associated with crypt injury) are a corroborating feature of suspected Crohn's after exclusion of identifiable infectious etiology, but reported prevalence in mucosal biopsies at time of first diagnosis varies. The likelihood of finding granuloma is a function of the number of specimens taken, the number of sections examined,

Table 2 Classic microscopic features in untreated ulcerative colitis (comparable Crohn's colitis, hard criteria)

Feature	Ulcerative colitis	Crohn's colitis
Diffuse	Continuous disease	Segmental disease
Rectal	Involvement	Variable rectal involvement
Disease	Worse distally	Variable disease severity
Fissures	No	Fissures, sinus, fistula
Transmural aggregates	No	Transmural lymphoid aggregates
Ileal involvement	No, exception during backwash ileitis	Ileal involvement Upper gastrointestinal involvement
Granulomas	No	Granulomas

and the definition of a granuloma. Granulomas occur more commonly in the submucosa than the mucosa[55]. Hence, they are observed in 60% of surgical specimens but relevant to the question of histology for diagnosis, in only 20%-40% of mucosal biopsies[55]. Moreover, according to Griffiths[38] data indicating clinical significance or prognostic value of presence or absence of granulomata are lacking.

Clinico-histopathologic findings in ulcerative colitis

The classic microscopic features in untreated UC (and CC hard criteria) used for diagnosis, as outlined by Odze[56], and are depicted in Table 2. Clinically, the hallmark of UC is hematochezia[57,58]. Additional clinical presentations include rectal tenesmus and incontinence, abdominal pain, severe inflammation of the rectum (proctitis), leukocytosis, hospitalization for total parenteral nutrition and/or intravenous fluids correction, among others. Blood transfusion and corticosteroids are recommended when considering surgery (RPC and IPAA)[58]. As mentioned earlier, in UC, inflammation is typically confined to the mucosal layer and to the lesser degree to the submucosa. Children with UC often have evidence of chronicity, rectal frugality, and little or no architectural warping. In otherwise usual cases of UC, these conditions may lead to a confusion with CC[59-61].

Current advances in biomarker discovery to delineate the colitides

To date, there has been significant interest in attempting to identify molecular biomarkers that can accurately delineate CC and UC phenotypes. These studies have been minimally successful at identifying such biomarkers. In serum these include: placenta growth factor-1 (PLGF-1), IL-7, TGFβ1, and IL-12P40[62-67]. In biopsies obtained from the mucosa, they are Rho GD1α, desmoglein, pleckstrin, VDAC (voltage-dependent anion channel), 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA), and C10orf76[68,69]. In stool they are calprotectin, PMN-elastate, lactoferrin, and S100A12[65,70-74]. Clearly these biomarbiometrics represent an advance in the field of colitides research and have been used for clinical prognostic trials but have not been shown to delineate UC from a CC phenotype[62,64,73,74]. Thus far, the above mentioned features reflect colitides intestinal inflammation and do not discriminate UC from the CC phenotype[65].

Histology-directed proteomic advances

Histology-directed MALDI MS is the first attempt ever used to analyze and compare mined proteins of the colonic mucosal and submucosal tissue layers individually, in order to differentiate between UC and CC[42,50]. The normal *topography* of the *colon* and the layers used in mining and extraction of analytical extracts are illustrated in Figure 1. The basic steps of the methodology of histology-directed mass spectral protein profiling are outlined in Figure 2. Specialized MALDI MS offers directly the possibility of direct proteomic assessment of the tissue itself. The histologic layers of colectomy samples from patients with histologically and clinically confirmed UC and CC, with no ambiguity, are analyzed individually using MALDI MS for proteomic profiling. The results have successfully identified highly significant MALDI MS mass-to-charge ratio (m/z) signals in colonic tissue layers that appear to be phenotype-specific and are likely to help distinguish UC and CC[42,50]. Pre-sequencing and identification proteomic pattern peaks from colonic mucosal or/and submucosal tissue section are depicted in Figure 3[50]. These signatures do not correlate to tissue of origin and thus represent disease-specific markers. Some of these are found in colonic mucosa, from which endoscopic biopsies could be subjected to proteomic analysis. Other signatures come from the submucosa and could be used for proteomic studies of serum. Other protein-signatures were found in both tissue layers. Identifying proteomic patterns characteristic of one specific colitis phenotype will significantly improve our understanding of the mechanistic events associated with IBD.

It is unlikely that a single protein or small cluster of proteins will have the necessary: (1) specificity; (2) sensitivity; (3) discrimination; and (4) predictive capacity, to differentiate the heterogeneity of IBD[69]. However, if it were possible, it would require a technology that can accommodate sampling large patient cohorts, while accounting for patient variability. MS is an important profiling and identification tool for such studies[75]. As necessary as the tool is, subsequent analysis and validation methods will determine the actual success of a detection system intended for non-invasive screening and evaluating treatment efficacy. The overall goal of delineating IBD by proteomics is to illuminate the pathobiology underlying the colitides. More

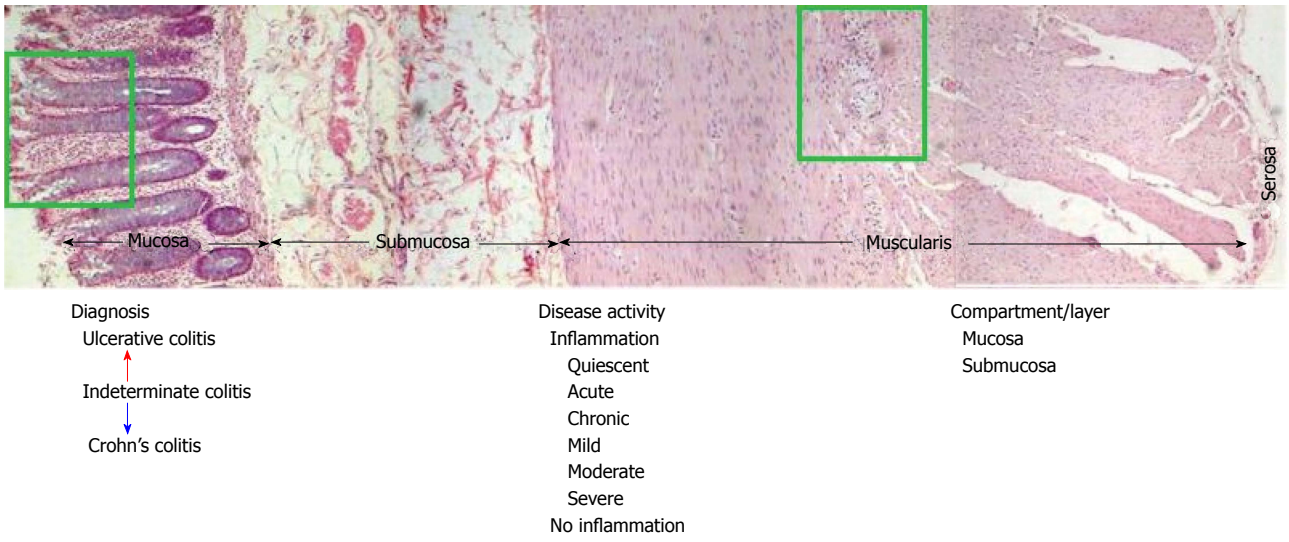

Figure 1 Human colon cross section depicts layers for mining proteomic patterns that delineates untreated ulcerative and Crohn's colitis phenotype. The colon is comprised of four distinct layers: (1) the mucosa; (2) the submucosa; (3) the muscularis (two thick bands of muscle); and (4) the serosa. Comparable proteomic patterns that are mined from these layers are analyzed, based on the diagnosis [untreated ulcerative and Crohn's colitis, (with no ambiguity)], disease activity and tissue layer.

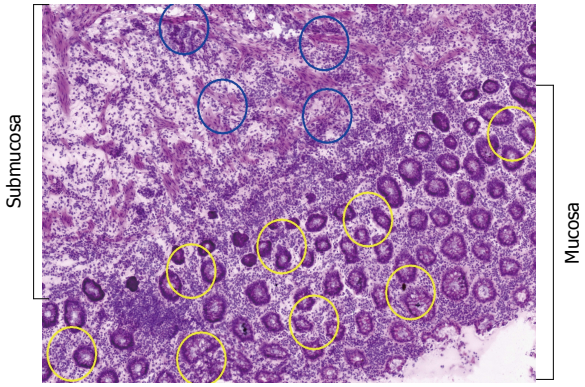

Figure 2 Histology-directed tissue layer profiling for matrix-assisted-laser desorption/ionization mass spectrometry. Digital photomicrographs acquired from histology and matrix-assisted-laser desorption/ionization sections were used to identify and designate sites of interest for profiling. Comparisons were performed in both the training and independent test set samples between inflamed mucosa Crohn's colitis (CC) *vs* ulcerative colitis (UC) and inflamed submucosa CC *vs* UC. Tissue section showing marked areas of pathological interest. Rings demonstrate matrix spots in mucosal and sub-mucosal layers (unpublished figure).

specifically, it is to identify patterns differentiating the colonic IBDs that exhibit overlapping clinical and histologic signs, but require different approaches of care. The anticipation is that this approach will eventually provide molecular biometrics of interest that can tell UC from CC through endoscopic biopsies and eventually create a serum biomarker tool assay for the identified peptide, if the protein(s) is (are) secretory and transposable. Better understandings of the bio-pathophysiologic mechanisms may allow new therapeutic and preventive avenues for maintenance or remission in IBD.

Matrix-assisted laser desorption/ionization MS

Specialized matrix-assisted laser desorption/ionization (MALDI) MS offers the possibility of direct proteomic assessment of the tissue itself[76]. The molecular specificity and sensitivity of MS can image and map biomolecules present in tissue sections. Applying complementary techniques of immunochemistry and fluorescence microscopy to MALDI MS data can improve the analysis of spatial arrangements of molecules within biological tissues. Accordingly, MALDI technology has become a popular in biology research. It combines two technologies, the MALDI "soft" ionization source and the TOF (Time of Flight) mass analyzer. The former volatilizes and ionizes molecules using a laser, a target, and an organic compound called a matrix, while the latter technology measures an ion's mass-to-charge ratio (m/z) by measuring the time it takes to reach a detector. MALDI TOF mass spectrometers come in two basic types: MALDI TOF MS and MALDI TOF/TOF MS. The latter enables tandem mass spectrometry (MS/MS) studies[69]. Thus a combination of markers may improve the chances of achieving IBD proteomics goals.

MS in combination with laser capture microdissection is another important profiling and identification tool for such studies. It allows direct tissue analysis of biomolecules and large organic molecules which are often too fragile for conventional ionization methods. These techniques may significantly enhance diagnostic accuracy and provide the basis for future bio-physiologic elucidations in IBD.

MALDI IMS

MALDI IMS stands out as a tool for imaging metabolites in the biological and medical fields, and as a new tool for pathology in the molecular age[77]. There are several advantages in IMS technology. First, IMS does not require labeling or specific probes. Second, it is a non-targeted imaging method, meaning unexpected metabolites can

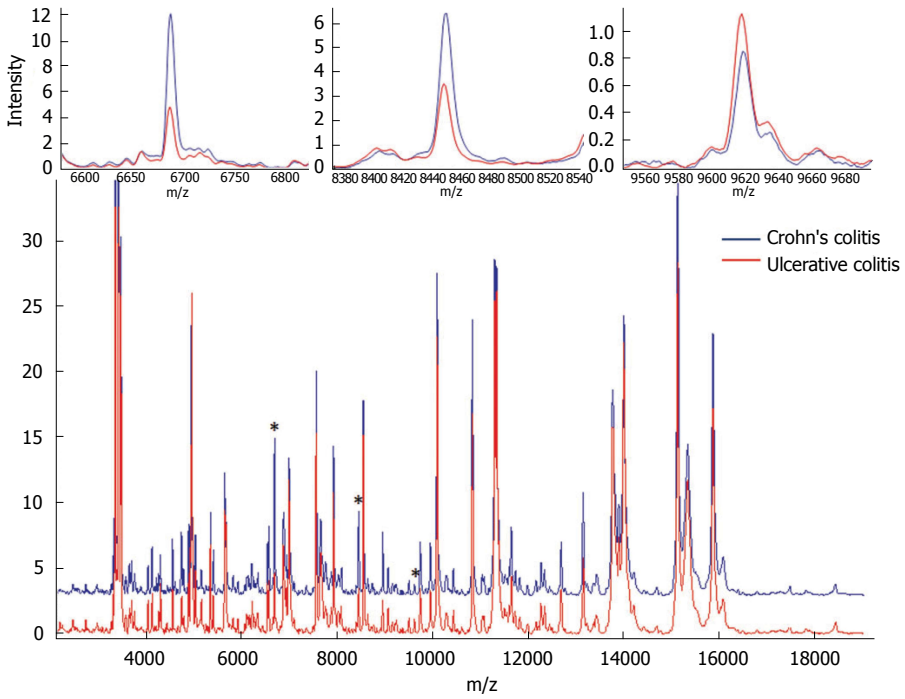

Figure 3 Show averaged mass spectrum proteomic pattern spectra from Crohn's colitis (blue) and ulcerative colitis (red). Differential distribution of three selected proteomic pattern peaks (m/z) obtained from colonic mucosal and/or submucosal tissue sections that were part of the Support Vector Machine model. They are denoted by "a" symbol in the full spectra. Reproduced with permission from the publisher: Seeley *et al*[50].

easily be imaged. Finally, several kinds of metabolites can be imaged simultaneously. The technique effectively provides a better visualization of the underlying mechanisms of biological processes of endogenous, small metabolites[78,79] and large proteins[80,81] in cells and tissues[82,83]. It can determine the distribution of hundreds of unknown compounds in a single measurement[79,84-86]. Further, IMS is capable of three-dimensional molecular images which can be combined with established imaging techniques like magnetic resonance imaging[87,88].

Due to the fact that the enormous molecular diversity of metabolite species is unknown, IMS technology is seemingly appropriate for localizing metabolites, whether they are from the molecule of interest or not[78,89,90]. The emerging technique of MALDI IMS has the capability to distinguish between parent and metabolites while maintaining spatial distribution in various tissues[91,92]. In spite of the promising advances of MALDI IMS for visual-imaging tiny metabolites, substantial concerns remain regarding its spatial resolution. The primary limitation results from the size/volume of the organic matrix crystal and analyte migration during the matrix application. There is also a lack of efficient computational techniques for constructing, processing, and visualizing large and complex 3D data which prevents experimenters from tapping its full potential[93]. In attempting to solve these important issues, researchers have devised another sophisticated method: a nanoparticle-assisted laser desorption/ionization (nano-PALDI)-based IMS, in which the matrix crystallization process is eliminated[94,95]. The use of novel nano-PALDI has enabled scientists to image compounds with spatial resolution at the cellular level (15 μmol/L; approximating the diameter of a laser spot)[96].

Serologic test advances

To date, a lack of validated information prevents recommending the use of serologic assays to screen general population patients for undiagnosed gastrointestinal symptoms in IBD-settings. As has been made clear, no unique biomarkers yet exist for the delineation between CC and UC. Serologic tests, antineutrophil cytoplasmic antibodies (ANCAs) and anti-microbial antibodies are inadequately sensitive and specific to contribute much to the diagnosis of CC or to its differentiation from UC.

ANCAs are immunoglobulin G (IgG) antibodies directed against cytoplasmic components of neutrophils[97]. The association with colitides of a subset of ANCA with a perinuclear staining pattern on immunofluorescence studies [perinuclear antineutrophil cytoplasmic autoantibodies (pANCA)] was first recognized for UC, where it was detected in 60%-70% of patients[97]. The specificity of perinuclear staining for colitides can be validated and confirmed by its disappearance after deoxyribonuclease (DNase) digestion of neutrophils. pANCA is considered a marker of the immunologic disturbance that underlies the development of chronic colonic inflammation, and should not be positive in acute self-limited, presumably infectious colitis.

Anti-*Saccharomyces cerevisiae* antibodies (ASCAs), the first anti-microbial antibodies to be described in CC, are IgG and IgA antibodies that recognize mannose sequences in the cell wall of *S. cerevisiae* strain Su1. ASCA is detected in 50%-70% of CC patients overall, 10%-15% of UC patients and in 5%-10% of controls with other

gastrointestinal disorders[97]. Newer anti-microbial antibodies (Abs), which include Abs against *Pseudomonas fluorescens*-associated sequence (anti-I2), anti-outer membrane protein C of *Escherichia coli* (anti-OmpC), anti-outer membrane protein of *Bacteroides caccae* (anti-OmpW), and anti-flagellin Abs (anti-CBir1), may result false positive and be detected in patients who otherwise have negative serology, but are nonspecific and can be detected in patients with other diseases[98,99].

Differentiation of CC from UC is clinically problematic because inflammation is only confined to the colon. pANCA is positive in up to 35% of patients with CC; ASCA is less often detected in patients with CC. Hence, the utility of combined ANCA/ASCA testing is less in the setting where it is needed most. In the one published study clearly reporting sensitivity, specificity, and predictive values of combined serologic testing, the sensitivity of ASCA+pANCA-serology for CC *vs* UC was only 32%[97]. In a long-term follow-up of patients with IC, Joossens *et al*[100] observed 26 patients who were ASCA+/pANCA- at baseline. Eight were later diagnosed with CC and 2 with UC, while the other 16 patients remained IC. The ASCA-/pANCA+ profile was even less helpful for definitive diagnosis[100].

When using upper GI biopsies, the differentiation between UC and CC is relatively straightforward in most of patients. In appropriate clinical settings, granulomatous inflammation in GI biopsies validates CC. In pediatric CC, granulomas may only be found in biopsies from the upper GI. Without routine upper endoscopy, these cases will be missed. If granulomas are not found, a diagnosis of CC or UC can be derived from endoscopic findings with histology combined with clinical and imaging determinations[101]. Determining cases of IBD as CC, UC, or IC is largely a matter of nomenclature. Supporting a determination with evidence from endoscopies, magnetic resonance enterography, or other techniques, improves clinical labelling of the condition. The colitides are a continuum between CC and UC, with a variety of inflammations between. Teasing out overlapping genetic profiles for UC and CC will be critical to applying correct treatment more accurately than using current nomenclature categories based on a current standard of histology[100]. Application and refinement of the above technologies and techniques will improve the possibility of approaching patients with individualized options reducing ineffective or unnecessary surgery. Usage of molecular biometrics to differentiate diseases of the same organ[38,102,103] is becoming ground breaking in improving diagnostic challenges in colonic IBD settings[42,50,104]. IBD has no permanent drug cure and results in significant morbidity and mortality[9,104,105]. UC is absolute colonic disease while CC can involve any part of the GI system from the mouth to the anus, which may transmurally involve partial to a full-thickness of the intestinal wall[43] and other organs through fistulization[106-108]. These diseases share several clinical biometric signatures but have different causes, mechanisms of tissue damage, and treatment options[16,109]. Therefore, accurate diagnosis is paramount for provision of correct pharmacologic therapy[110,111] and surgical care[112-114].

CONCLUSION

The term "colitides" characterizes colonic IBD and comprises ulcerative colitis and Crohn's colitis (UC and CC). The etiopathogenesis of UC and CC remains enigmatic. Diagnostic accuracy for distinguishing these two pathologies is still a significant problem in GI medicine and is hindered by a growing overlap of histopathological interpretation. Despite all efforts, many patients continue to remain undetermined as UC or CC, and are said to have indeterminate colitis. Differentiations of UC and CC are concluded from imprecise clinical, histopathologic, and other examinations. This results in speculative colitis staging and severity which cannot be conclusively differentiated in up to 30% of patients with IBD. CC and UC diagnostic features often overlap[115] even after a thorough histological assessment, the current gold-standard for distinguishing type of inflammation (for CC: lack of non-specific inflammation not confined beyond mucosa and diffused or focal granulomatous *etc*. For UC: inflammation limited to the mucosa, diffuse infiltration of acute and chronic inflammatory cells in the mucosa, continuous damage from the rectum to proximal colon, *etc*.).

Treatment options for UC and CC differ significantly. Thus appropriate individualized prognosis and treatment requires accurate diagnosis. An estimated 90% of patients with IC undergo pouch surgery (RPC and IPAA) for fulminant colitis[36,48,49,115,116] contrasting with 30% of patients in whom UC or CC was a correct diagnosis. Additionally, failure to recognize specific indicators of CC (*e.g*., granulomas and transmural inflammation) often leads to mistakes in pathological interpretation[24,36]. This results in a reciprocal misdiagnosis rate of 15% (CC as UC: UC as CC). Adding = the 15% of cases labeled as IC accounts for nearly a third of the all IBD patients. Those undergoing surgery for a presumably confirmed diagnosis of UC subsequently are diagnosed postoperatively with recurrent CC in the ileal pouch[36]. This is critical because functional failure and higher complication rates are estimated at up to 60%[35,117-123] and often require excision of the pouch with a permanent end ileostomy[35,121-124]. At this stage, patient health quality of life is significantly jeopardized for life.

There has been wide ranging interest in attempting to identify molecular biomarkers that can consistently delineate these diseases. These studies have been minimally successful at identifying quiescent or active IBD in serum[62-67], in mucosal biopsies[68,69], and in fecal matter[65,70-74]. Clearly these features represent an intriguing advance in the science of IBD for clinical disease prognostic purposes. However, these markers have not been shown to distinguish UC from CC phenotype[62,64,73,74]. A serology panel including ANCA, pANCA, anti-saccharomyces cerevisae IgG and IgA antibodies (ASCA), calgranulin (S100A12), anti-OmpC antibodies, fecal lactoferrin, calprotectin, and polymorphonuclear neutrophil

elastase (PMN-e)[65] is marketed as a promising approach to monitor disease activity and prognosis and may prove to be beneficial in the management of IBD. The specificity, sensitivity and diagnostic accuracy of these parameters with reference to clinical disease indices and/or endoscopically measured inflammation in IBD setting remain unclear. What we have learned to date is that: (1) Although not yet commercially available as tests, patients with CC are more likely than healthy control and/or IBD patients to be positive for a range of biomarkers such as S100A12 (calgranulin), ASCA, OmpC, CBir1, pseudomonas fluorescens protein, and pANCA[125,126]. Significant increases of these proteins are noted during active intestinal inflammation. The greater the number of positive serologies and the higher the titer, the more aggressive the course. These biomarkers are also seen in an active UC[127]; (2) A combination of these biomarkers and a disease-specific activity index could promote the diagnostic accuracy in clinical medicine with reference to endoscopic inflammation but at present none are superior in the ability to reflect endoscopic inflammation[70]; (3) These molecular biometrics significantly assist in predicting relapses in patients with confirmed IBD (active or quiescent)[2-5,17,21,128] but are not discriminatory between UC/CC; (4) Patients who are pANCA+ and ASCA- are more likely to have UC than CC, while in pANCA- and ASCA+ patients the reverse may be true[67]. However, these biomarkers have not demonstrated clinical utility as predictors or monitoring tools of IBD activity[67].

At the present time there is insufficient biometric information to recommend use of serologic assays in screening for IBD in patients from the general population who have undiagnosed gastrointestinal symptoms. Further, no efficacy for the delineation of CC and UC clearly exist.

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MINIREVIEWS

Medical management of patients after bariatric surgery: Principles and guidelines

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Abstract

Obesity is a major and growing health care concern. Large epidemiologic studies that evaluated the relationship between obesity and mortality, observed that a higher body-mass index (BMI) is associated with increased rate of death from several causes, among them cardiovascular disease; which is particularly true for those with morbid obesity. Being overweight was also associated with decreased survival in several studies. Unfortunately, obese subjects are often exposed to public disapproval because of their fatness which significantly affects their psychosocial behavior. All obese patients (BMI $\geqslant$ 30 kg/m^2) should receive counseling on diet, lifestyle, exercise and goals for weight management. Individuals with BMI $\geqslant$ 40 kg/m^2 and those with BMI > 35 kg/m^2 with obesity-related comorbidities; who failed diet, exercise, and drug therapy, should be considered for bariatric surgery. In current review article, we will shed light on important medical principles that each surgeon/gastroenterologist needs to know about bariatric surgical procedure, with special concern to the early post operative period. Additionally, we will explain the common complications that usually follow bariatric surgery and elucidate medical guidelines in their management. For the first 24 h after the bariatric surgery, the postoperative priorities include pain management, leakage, nausea and vomiting, intravenous fluid management, pulmonary hygiene, and ambulation. Patients maintain a low calorie liquid diet for the first few postoperative days that is gradually changed to soft solid food diet within two or three weeks following the bariatric surgery. Later, patients should be monitored for postoperative complications. Hypertension, diabetes, dumping syndrome, gastrointestinal and psychosomatic disorders are among the most important medical conditions discussed in this review.

Key words: Obesity; Bariatric surgery; Postoperative care; Body-mass index; El banna

Core tip: Obesity is a growing health concern worldwide that impacts the life of individuals both physically and psychologically. There are several well-established health hazards associated with obesity. Additionally, obese subjects are often exposed to public disapproval because of their fatness which significantly affects their psychosocial behavior. Bariatric surgery is one of the definite solutions for obesity. In this review, we will briefly discuss the general guidelines that should be considered before bariatric surgery. Also, we discuss the protocols of patients' postoperative care and the management of medical disorders that must be considered after bariatric surgery.

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INTRODUCTION

Obesity is a chronic disease that impairs health-related quality of life in adolescents and children. In 2010, overweight and obesity were estimated to cause 3.4 million deaths, 3.9% of years of life loss, and 3.8% of disability-adjusted life-years worldwide. Obesity is increasing in prevalence, currently, the proportion of adults with a body-mass index (BMI) of 25 kg/m^2 or greater is 36.9% in men and 38.0% in women worldwide[1]. Attempts to explain the large increase in obesity in the past 30 years focused on several potential contributors including increase in caloric intake, changes in the composition of diet, decrease in the levels of physical activity and changes in the gut microbiome. More than 50% of the obese individuals in the world are located in ten countries (listed in order of number of obese individuals): United States, China, India, Russia, Brazil, Mexico, Egypt, Germany, Pakistan and Indonesia. Although age-standardized rates were lower in developing than in developed countries overall, 62% of the world's obese individuals live in developing countries. Recently, United States accounted for 13% of obese people worldwide, the prevalence of obesity was 31.7% and 33.9% among adult men and women, respectively. In Canada 21.9% of men and 20.5% of women are obese. Reported prevalence rates of obesity include: 27.5% of men and 29.8% of women in Australia, 24.5% of men and 25.4% of women in the United Kingdom, in Germany 21.9% of men and 22.5% of women, in Mexico 20.6% of men and 32.7% of women, in South Africa 13.5% of men and 42% of women, in Egypt 26.4% of men and 48.4% of women, in Saudi Arabia 30% of men and 44.4% of women and in Kuwait 43.4% of men and 58.6% of women (Table 1, Figure 1)[2]. There are several well-established health hazards associated with obesity, *e.g.,* nonalcoholic steatohepatitis (NASH), type 2 diabetes, heart disease, chronic kidney disease, gastroesophageal reflux disease, gastrointestinal motility disorders, sexual disorders, cerebrovascular stroke, certain cancers, osteoarthritis, depression and others[3-10]. The risk of development of such complications rises with the increase of adiposity, while weight loss can reduce the risk. Bariatric surgery could be the definitive clue in many situations[11-15]. Bariatric surgery is one of the fastest growing operative procedures performed worldwide, with an estimated > 340000 operations performed in 2011. While the absolute growth rate of bariatric surgery in Asia was 44.9% between 2005 and 2009, the numbers of procedures performed in the United States plateaued at approximately 200000 operations per year[16,17]. Starting in 2006, the Center for Medicare and Medicaid Services, United States, restricted the coverage of bariatric surgery to hospitals designated as "Centers of Excellence" by two major professional organizations[18]. Medical management and follow up of patients who have undergone bariatric surgery is a challenge due to post operative complications.

GENERAL GUIDELINES FOR SURGEONS/ GASTROENTEROLOGISTS

A well skilled physician or a surgeon has to consider the followings: (1) as the prevalence of obesity increases so does the prevalence of the comorbidities associated with obesity. Losing weight means overcoming illness at the present, complications in future and alleviating the economic burden in the present and future; (2) Overweight; BMI between 25 and 30, technically refers to excessive body weight, whereas "obesity" BMI $\geqslant$ 30 kg/m^2 refers excessive body fat, "Severe obesity", BMI $\geqslant$ 35 kg/m^2, or "morbid obesity" refers to individuals with obesity-related comorbidities. Furthermore, severe obesity and morbid obesity groups who failed dietary and medical regimens are candidates for bariatric surgery; (3) Children obesity; refers to children with BMI > 95th percentile for their age and sex and "overweight" refers to children with BMI between the 85th and 95th percentile for their age and sex; (4) Patients undergoing a bariatric operation should have a nutritional assessment for deficiencies in macro and micronutrients, also with no contraindication for such a major operation; (5) Most of bariatric procedures are performed in women (> 80%) and approximately half of these (> 40% of all bariatric procedures) are performed in reproductive aged women, accordingly, pregnancy planning and contraception options should be discussed in details with women who will undergo bariatric procedures. Fertility improves soon after bariatric surgery, particularly in middle-aged women, who were anovulatory. Additionally, oral contraceptives may be less effective in women who have undergone malabsorptive bariatric procedure. Therefore, it is better to delay pregnancy for 6-12 mo following bariatric surgery. Risk of preeclampsia, gestational diabetes, and macrosomia significantly decrease post bariatric surgery, but the risk of intrauterine growth restriction/small infants for their gestational age may increase. Body contouring surgery is in high demand following bariatric surgery; (6) All bariatric operations are accompanied with restrictive and/or malabsorption maneuvers; less food intake and malabsorption concepts; (7) The most common types of bariatric surgeries performed worldwide are Sleeve gastrectomy (SG): This procedure involves the longitudinal excision of the stomach and thus shaping the remaining part of the stomach into a tube or a "sleeve" like structure. SG removes almost 85% of the stomach (Figure 2); Roux-en-Y gastric bypass (RYGB): It reduces the size of the stomach to the size of a small pouch that is directly surgically attached to the lower part of the small intestine. In this procedure, most of the stomach and the duodenum are surgically stapled and therefore, bypassed (Figure 3); The laparoscopic adjustable gastric band (AGB): This is one of the least invasive procedures,

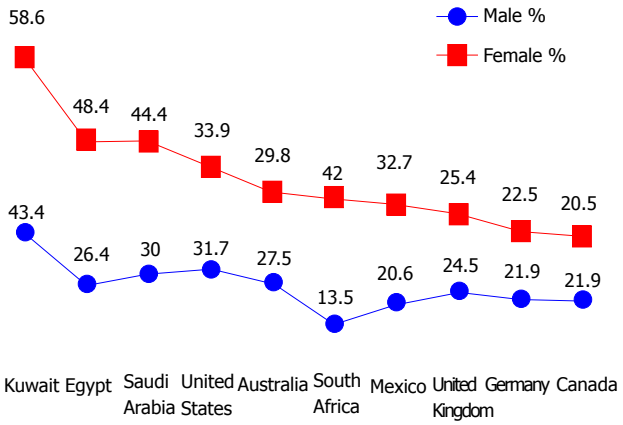

Figure 1 Male to female prevalence in different countries worldwide.

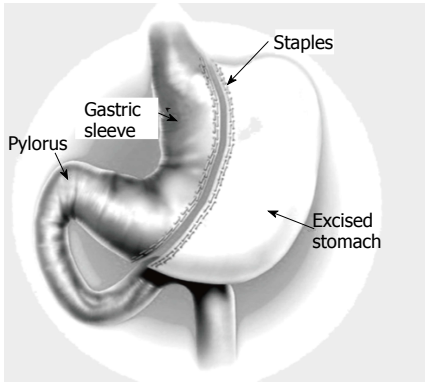

Figure 2 Schematic presentation of sleeve gastrectomy.

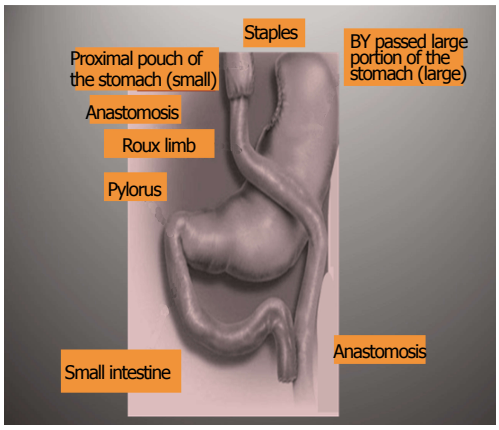

Figure 3 Schematic presentation of Roux-in Y Gastrectomy.

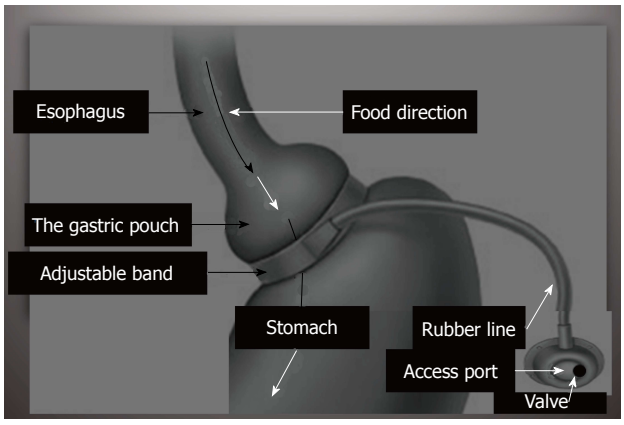

Figure 4 Schematic presentation of adjustable gastric band.

where the surgeon inserts an adjustable band around a portion of the stomach and therefore, patients feel fuller after eating smaller food portions (Figure 4). Bariatric surgical procedures, particularly RYGB, plus medical therapy, are effective interventions for treating type 2 diabetes. Improvement in metabolic control is often evident within days to weeks following RYGB; and (8) Complications reported following bariatric surgery vary based upon the procedure performed. Cholilithiasis, renal stone formation and incisional hernia could be the delayed phase complications; on the other hand, bleeding, leaking, infection and pulmonary embolism could be the early phase complications following the bariatric procedure. The overall 30-d mortality for bariatric surgical procedures worldwide is less than 1%.

POST OPERATIVE CARE AND FOLLOW UP

Early post operative period; (1-3) d post bariatric surgery

Patients undergoing a bariatric operation are admitted to the post-anesthesia care unit (PACU) immediately at the conclusion of the operation. Usually, on postoperative day (POD) one, we begin oral therapy in tablet or crushed-tablet and liquid form if there is a naso-gastric tube after the gastrografin leak test. A basic metabolic profile (*e.g.,* complete blood count, electrolytes, renal function, liver function, prothrombin time and partial thromboplastin time) should be obtained every 12 h for the successive two PODs, then every 24 h for another 3 d. Oxygen is administered by nasal cannula and weaned thereafter. The likelihood that, early specific complication, will arise for a given patient is determined by the nature of the procedure, the anesthetic techniques used, and the patient's preoperative diseases. Respiratory problems are common complication in the early postoperative period following bariatric surgery. Patients with significant comorbidities, particularly neuromuscular, pulmonary, or cardiac problems are at a higher risk for respiratory compromise, but any patient can develop hypoxemia following bariatric surgery. For prophylaxis against Deep Venous Thrombosis (DVT) following bariatric surgeries, ultrasound evaluation is recommended for all patients, D-dimer test should be applied for suspected patients with DVT, especially after long operative time, repeat ultrasound or venography may be required for those with suspected calf vein DVT and a negative initial ultrasound investigation[19,20].

Late post operative monitoring

After the PACU period, most patients are transferred to the inpatient surgical postoperative unit. For the next 24-72 h, the postoperative priorities include ruling out an

Table 1 Prevalence of obesity in different countries worldwide

Country	Male	Female
United States	31.70%	33.90%
Canada	21.90%	20.50%
United Kingdom	24.50%	25.40%
Australia	27.50%	29.80%
Germany	21.90%	22.50%
Mexico	20.60%	32.70%
South Africa	13.50%	42%
Egypt	26.40%	48.40%
Saudi Arabia	30%	44.40%
Kuwait	43.40%	58.60%

anastomotic leak following laparoscopic RYGB or laparoscopic SG. If no leak is observed, patients are allowed to start a clear liquid diet and soft drinks. The postoperative care team cares for the following: control of pain, care of the wound, continuous monitoring of blood pressure, intravenous fluid management, pulmonary hygiene, and ambulation. Post-bariatric nausea and vomiting is directly correlated with the length of the surgery; it also increases in females, non-smokers, and those patients with prior history of vomiting or motion sickness. Prophylaxis with pharmacologic treatment before the development of post operative nausea and vomiting significantly reduces its incidence after surgery[21-23].

After hospital discharge

Diet: Usually patients are discharged 4-6 d after surgery. Most patients are typically discharged from the hospital on a full liquid diet, patients should be taught to keep monitoring their hydration and urine output. Approximately two-three weeks after surgery, the diet is gradually changed to soft, solid foods. The average caloric intake ranges from (400) to (800) kcal/d for the first month, and thus the daily glycemic load is greatly reduced. We encourage patients to consume a diet consisting of salads, fruits, vegetables and soft protein daily.

To control the epigastric pain and vomiting, patients should be taught to eat slowly, to stop eating as soon as they reach satiety and not to consume food and beverages at the same time. For most patients suffering chronic vomiting, prokinetic therapy and proton-pump inhibitors (PPIs) should be considered. Patients, who underwent SG, LAGB or RYGB, benefit from a well-planned dietary advancement. Patients should understand that the surgery has changed their body but not the environment, they have to choose healthy foods, do not skip meals and to visit the dietitian regularly in the first 12 mo after surgery. However, if food intolerance develops, patients may choose a more vegetarian-based diet. Nevertheless, fresh fruits and vegetables are usually tolerated without a problem. The daily protein intake should be between 1.0 to 1.5 g/kg ideal body weight per day[24]. The biliopancreatic diversion/duodenal switch (BPD/DS) is a malabsorptive procedure for both macro- and micronutrients. Hence, we encourage higher protein intake of 1.5 g to 2.0 g of protein/kg ideal body weight per day, making the average protein requirement per day approximately 90 g/d[25,26]. Alcohol is better prevented in the first 6-12 mo after surgery[27].

Monitoring: Patients should generally have their weight and blood pressure measured weekly until the rapid weight loss phase diminishes, usually within 4-6 mo, then again at 8, 10 and 12 mo, and annually thereafter. Patients with diabetes are encouraged to check their blood glucose daily. Glycemic control typically improves rapidly following bariatric surgery. Patients maintained on antihypertensive or diabetic medications at discharge should be monitored closely for hypotension and hypoglycemia, respectively, and medications should be adjusted accordingly. We recommend that the following laboratory tests be performed at three, six, nine months and annually thereafter: (1) Complete Blood Count; (2) Electrolytes; (3) Glucose and Glucose Tolerance test; (4) Complete iron studies; (5) Vitamin B12; (6) Aminotransferases, alkaline phosphatase, bilirubin, GGT; (7) Total protein and Albumin; (8) Complete lipid profile; (9) 25-hydroxyvitamin D, parathyroid hormone; (10)Thiamine; (11) Folate; (12) Zinc; and (13) Copper.

Complications following the surgical treatment of severe obesity vary based upon the procedure performed. Secondary hyperparathyroidism, Hypocalcemia, Gastric remnant distension, Stomal stenosis/Obstruction, Marginal ulcerations, Cholilithiasis, Ventral incisional hernia, Internal hernia, Hiatus Hernia, Short bowel syndrome, Renal failure, Gastric prolapse, infection, Esophagitis, Reflux, Vomiting, Hepatic abnormalities and dumping syndrome are common late-phase complications after bariatric surgery. However, the clinician should aware of complications specific for every bariatric procedure[28,29]. Before therapy, the clinician should understand that the impact of various bariatric surgeries on drug absorption and metabolism are scarce. On the other hand, RYGB and other malabsorptive procedures that significantly exclude the proximal part of the small intestine, decrease the surface area where most drug absorption occurs and may result in a reduction in systemic bioavailability[30-32].

COMMON MEDICAL CONDITIONS FOLLOWING BARIATRIC SURGERY

Hypertension

Hypertension is not always related to obesity, and dietary interventions do not assure the normalization of blood pressure. However weight loss, whether by an intensive lifestyle medical modification program or by a bariatric operation, improves obesity-linked hypertension. Patients should be monitored weekly until the blood pressure has stabilized, and patients may need to resume antihypertensive medications, but often at adjusted doses[33].

Diabetes

Patients with diabetes should have frequent monitoring of blood glucose in the early postoperative period

and should be managed with sliding scale insulin. Many diabetic patients have a decreased need for insulin and oral hypoglycemic agents after bariatric surgery. Oral sulfonylureas and meglitinides should be discontinued postoperatively as these medications can lead to hypoglycemia after bariatric surgery. Metformin is the safest oral drug in the postoperative period, since it is not associated with dramatic fluctuations in blood glucose. RYGB is associated with durable remission of type 2 diabetes in many, but not all, severely obese diabetic adults. However those who underwent LAGB generally exhibit a slower improvement in glucose metabolism and diabetes as they lose weight in a gradual fashion[34,35].

Reflux

Medications for gastroesophageal reflux disease (GERD) may be discontinued after RYGB and Laparoscopic AGB, however, SG has been associated with an increased incidence of GERD in some procedures. Recurrent GERD symptoms after RYGB, particularly when accompanied by weight regain, should raise the possibility of a gastrogastric fistula between the gastric pouch and remnant, and should be investigated by an upper GI contrast study or CT scan and referred to the bariatric surgeon. Upper endoscopy is the best investigation to exclude other esophagogastroduodenal disorders. GERD may be associated with esophageal complications including esophagitis, peptic stricture, Barrett's metaplasia, esophageal cancer and other pulmonary complications. Failure of the PPI treatment to resolve GERD-related symptoms has become one of the most common complications of GERD after bariatric surgery. Most patients who fail PPI treatment have Non Erosive Reflux Disease and without pathological reflux on pH testing. In patients with persistent heartburn despite of medical therapy, it is reasonable to recommend avoidance of specific lifestyle activities that have been identified by patients or physicians to trigger GERD-related symptoms[36-38].

Nausea and vomiting

Nausea and vomiting can often be helped by antiemetic or prokinetic drugs, however, some patients have chronic functional nausea and/or vomiting that does not fit the pattern of cyclic vomiting syndrome or other gastrointestinal disorders, hence particular attention should be directed to potential psychosocial factors post bariatric surgery. Therefore, low dose antidepressant medications and psychotherapy should be addressed. On demand CT scan and Gastroscopy could be the gold standard investigations in chronic situations[39,40].

Marginal ulceration

Due to increased risk of ulcer formation from nonsteroidal anti-inflammatory drugs (NSAIDs), these medications should be discontinued postoperatively, especially after RYGB. NSAID use is associated with an increased risk of bleeding. If analgesic or anti-inflammatory treatment is needed, the use of acetaminophen is preferred in a dose of 1-2 g/daily[41-45]. Other factors associated with increased risk of ulcer formation are smoking, alcohol, spicy food, gastrogastric fistulas, ischemia at the site of surgical anastomosis, poor tissue perfusion due to tension, presence of foreign material, such as staples and/or Helicobacter pylori infection. Diagnosis is established by upper endoscopy. According to our strategy, all patients should undergo diagnostic upper endoscopy to exclude congenital or GI diseases prior to bariatric procedures. Medical management is usually successful and surgical intervention is rarely needed[46-48].

DUMPING SYNDROME

Dumping syndrome or rapid gastric emptying is a group of symptoms that most likely occur following bariatric bypass. It occurs when the undigested contents of the stomach move too rapidly into the small intestine. Many patients who underwent bariatric bypass experienced postprandial hypoglycemia. However, the dumping syndrome usually occurs early (within one hour) after eating and is not associated with hypoglycemia. It is presumed to be caused by contraction of the plasma volume due to fluid shifts into the gastrointestinal tract. Dumping syndrome may result in tachycardia, abdominal pain, diaphoresis, nausea, vomiting, diarrhea, and sometimes, hypoglycemia. The late dumping syndrome is a result of the hyperglycemia and the subsequent insulin response leading to hypoglycemia that occurs around 2-3 h after a meal. Dumping syndrome is a common problem that occurs in patients who have undergone RYGB and when high levels of simple carbohydrates are ingested. Accordingly, patients who have experienced postgastric bypass bariatric surgery should avoid foods that are high in simple sugar content and replace them with a diet consisting of high fiber and protein rich food. Eating vegetables and salad is encouraged; beverages and alcohol consumption are better avoided[49].

PSYCHOSOMATIC DISORDERS/ DEPRESSION

Many patients usually experience enhanced self esteem and improved situational depression following weight loss. Depression often requires continued treatment, specially that, many patients with severe obesity often use food for emotional reasons. Therefore, when those patients experience a small gastric pouch postoperatively they may grieve the loss of food. Many studies documented the relationship between eating disorder and anxiety disorder, depression or schizophrenia[50,51]. Displaced emotions can result in somatization with symptoms of depression and psychosomatic disorders. It is important that clinicians recognize the psychological aspect of food loss after bariatric surgery, and reassure patients that the symptoms are related to the small gastric pouch size. Antidepressants often help to decrease the anxiety related to grieving associated with food loss, although the

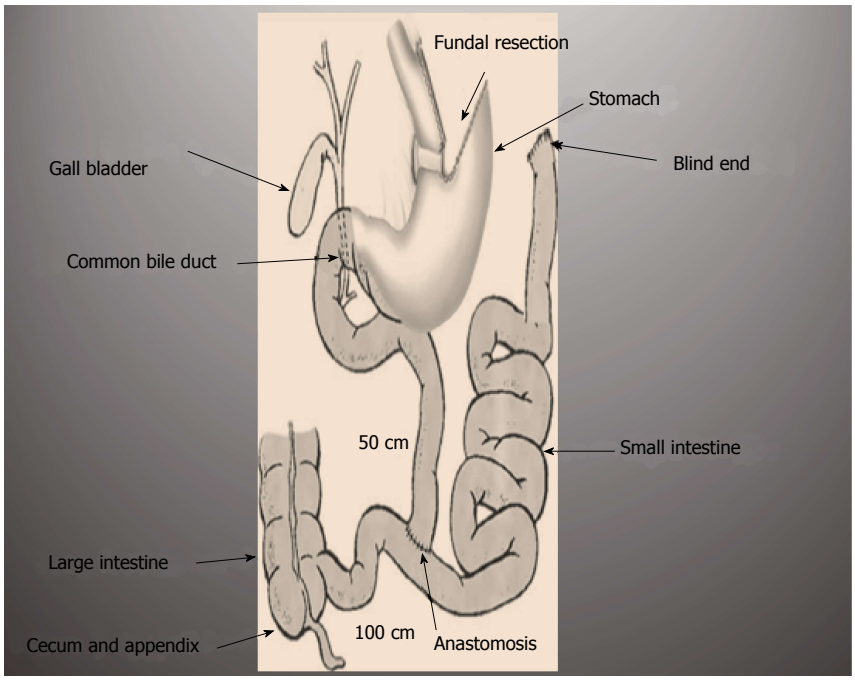

Figure 5 Novel Elbanna surgical procedure.

use of antidepressants needs to be approached with an empathetic style. Behavioral and emotive therapies are reported to be very helpful[52,53].

OUTCOME

Bariatric surgery remains the only effective sustained weight loss option for morbidly obese patients. The American Society for Metabolic and Bariatric Surgery estimated that in 2008 alone, about 220000 patients in the United States underwent a weight loss operation. The optimal choice for type of bariatric procedure, *i.e.*, RYGB, SG, AGB or the selected surgical approach, *i.e.,* open versus laparoscopic depends upon each individualized goals, *i.e.*, weight loss, glycemic control, surgical skills, center experience, patient preferences, personalized risk assessment and other medical facilities. Laparoscopic sleeve gastrectomy is the most common bariatric procedure. However weight re-gain after long-term follow-up was reported[54-58]. Prospective studies and reviews report a general tendency for patients with metabolic disorders to improve or normalize after bariatric surgery. However weight loss is highly variable following each procedure. Recent studies have evaluated the potential impact of obesity on outcomes in organ-transplant recipients, for example bariatric surgery may be an important bridge to transplantation for morbidly obese patients with severe heart failure[59-63].

RECENT ADVANCES IN BARIATRIC SURGERY

A modified intestinal bypass bariatric procedure (Elbanna operation), reported a novel surgical technique designed to maintain good digestion, better satiety, and selective absorption with less medical and surgical complications (Figure 5). This procedure preserves the proximal duodenum and the terminal ileum and thus preserving the anatomical biliary drainage and enterohepatic circulation[64,65].

Recently, a novel bariatric technique dedicated; Modified Elbanna technique in childhood bariatric, showed promising success in pediatric surgeries (non published data).

CONCLUSION

The rising prevalence of overweight and obesity in several countries has been described as a global pandemic. Obesity can be considered like the driving force towards the pre-mature deaths. It increases the like hood for the development of diabetes, hypertension and NASH. The American Heart Association identified obesity as an independent risk factor for the development of coronary heart disease. In order to minimize post-surgical cardiovascular risk, surgical weight loss may become a more frequently utilized option to address obesity. Currently, bariatric surgery passes through a plateau phase, hence medical management and follow up of patients who have undergone bariatric surgery is a challenge.

FUTURE RECOMMENDATIONS

Children obesity has become one of the most important public health problems in many industrial countries. In the United States alone, 5% of children have severe obesity. It is imperative that health care providers should identify overweight and obese children so as to start early counseling and therapy. To establish a therapeutic relationship and enhance effectiveness, the communication and interventions should be supported by the entire family, society, school, public media and primary health care. Bariatric surgery could be considered in complicated cases that failed all other options.

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OBSERVATIONAL STUDY

Factors influencing the diagnostic accuracy and management in acute surgical patients

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Abstract

AIM: To evaluate the diagnostic accuracy (DA) in acute surgical patients admitted to a District General Hospital.

METHODS: The case notes of all acute surgical patients admitted under the surgical team for a period of two weeks were reviewed for the data pertaining to the admission diagnoses, relevant investigations and final diagnoses confirmed by either surgery or various other diagnostic modalities. The diagnostic pathway was recorded from the source of referral [general practitioner (GP), A and E, in-patient] to the correct final diagnosis by the surgical team.

RESULTS: Forty-one patients (23 males) with acute surgical admissions during two weeks of study period were evaluated. The mean age of study group was 61.05 ± 23.24 years. There were 111 patient-doctor encounters. Final correct diagnosis was achieved in 85.4% patients. The DA was 46%, 44%, 50%, 33%, 61%, 61%, and 75% by GP, A and E, in-patient referral, surgical foundation year-1, surgical senior house officer (SHO), surgical registrar, and surgical consultant respectively. The percentage of clinical consensus diagnosis was 12%. Surgery was performed in 48.8% of patients. Sixty-seven percent of GP-referred patients, 31% of A and E-referred, and 25% of the in-patient referrals underwent surgery. Surgical SHO made the most contributions to the primary diagnostic pathway.

CONCLUSION: Approximately 85% of acute surgical patients can be diagnosed accurately along the diagnostic pathway. Patients referred by a GP are more likely to require surgery as compared to other referral sources. Surgical consultant was more likely to make correct surgical diagnosis, however it is the surgical SHO that contributes the most correct diagnoses along the diagnostic pathway.

Key words: Diagnostic accuracy; Diagnostic error; Misdiagnosis; Premature closure

Core tip: Approximately 85% of acute surgical patients can be diagnosed accurately along the diagnostic pathway. One of the strategies to reduce diagnostic error is to develop pathways for feedback. It is particularly important to develop feedback pathways for the junior doctors, as it has been shown that less experienced doctors tend to most over-estimate their diagnostic accuracy. With anonymity removed, the basic design of this study seems well suited to enable feedback to each physician involved in the care of an acute surgical patient.

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INTRODUCTION

Diagnostic errors have recently begun to receive more attention as a preventable source of patient harm. Diagnostic errors are estimated to account for 80000-160000 deaths per year[1]. Misdiagnosis has been the leading cause of medical malpractice payments over the last 25 years, making up 28.6% of claims and 35.2% of total payouts[1]. Missed, incorrect, or delayed diagnoses are estimated to occur in 15% of clinical cases, accounting for 8%-20% of adverse medical events[2]. Diagnosis is the most critical of a physician's skills. Nuland previously so perfectly stated, "It is every doctor's measure of his abilities; it is the most important ingredient in his professional self image"[3], yet even with such a high regard for diagnostic accuracy, there remains an absence of ownership when it comes to quality and safety systems to reduce the diagnostic errors[4]. Most of the studies attempting to quantify the diagnostic error have either been retrospective studies examining adverse events, such as malpractice claims and autopsy reports, or have been experimental studies comparing multiple physician responses to the same diagnostically challenging scenarios, which are often not reflective of the actual clinical environment[2]. Therefore, the true prevalence of diagnostic errors and inability to make right diagnosis along the acute surgical pathway has been notoriously difficult to evaluate[2,5].

Preventable diagnostic errors can result form the system-related factors and various cognitive factors. A published article on the prevalence of diagnostic error in 100 clinical cases revealed the system-related factors result in 65% diagnostic inaccuracies and cognitive factors in 74%[6] of the diagnostic inaccuracies. While many programs have been initiated to address the system-related factors such as improved communication, enhancing the concept of an effective teamwork, and tackling the procedural problems, clear pathways to reduce the diagnostic errors contributed by the cognitive factors have been more elusive and indefinable. A wide range of suggestions have been made about how to reduce cognitive errors in making the correct diagnosis. Graber *et al*[6] have described three distinct categories of interventions as those meant to: (1) improve knowledge and experience; (2) improve clinical reasoning and decision-making skills; and (3) provide cognitive "help". Though many of these suggestions are well conceptualized and widely endorsed, a large portion remain untested or testing has been restricted to trainees in artificial settings, which does not necessarily reflect actual practice[7]. The diagnostic pathway for acute surgical patients involves GPs, Accident and Emergency, and surgeons. The need to investigate and quantify the impact of procedural and diagnostic accuracy at each level of medical contact is clear. Lack of a working diagnosis impacts patient care, outcome, and cost.

The objective of this observational study is to evaluate the diagnostic accuracy at each level of the primary diagnostic pathway in acute surgical patients admitted to a District General Hospital.

MATERIALS AND METHODS

Study conception

It was noted that ward rounds for on-call surgeons were often disorganized, with no clear roles defined, leading to inconsistent record keeping. Therefore, on call surgical team decided to address this by running ward rounds using briefing and debriefing for each ward round, rotating roles (each person present taking turns with patient presentation, record-keeping, and drug chart review), and asking each member of the team if they had anything to add before moving to the next patient. The surgical team was encouraged to clearly record 3 differential diagnoses for each doctor-patient encounter. It became apparent that the differential diagnoses listed would often change along the primary diagnostic pathway, and the idea to survey these changes emerged.

Profroma

A one-page profroma was designed and relevant variables reported in previous but similar publications were inserted on it. Because this was an observational and pilot study examining the performance of the acute surgical team without any involvement of the patients, therefore, only an informal approval of the study was taken from the local Ethics and Research Committee with verbal discussion and electronic communication. The contents of the profroma were presented in internal clinical governance meeting and few additional variables were also included based upon the recommendations of clinical governance panel. All authors and local Ethics and Research Committee approved the profroma and its contents before starting the data collection.

Inclusion criteria

To review the case notes and ward round entries of all acute surgical admissions during randomly selected two weeks.

Exclusion criteria

Patients whose notes were not available through secretaries or on the wards during data collection were excluded.

Data collection

Patient information including surname, hospital number, date of birth, and gender was collected onto a one page proforma, and each doctor/patient encounter was reviewed retrospectively to include up to 3 differential diagnoses listed in the patient notes. Doctors were anonymously recorded as general practitioner (GP), accident and emergency doctor (A and E), in-patient referrer (IP), surgical foundation year-1, surgical senior house officer (SHO), surgical registrar on-call (SROC), and the surgical consultant. Patient/doctor encounters were recorded along the primary diagnostic pathway, from GP referral, if available, up to the first surgical consultant review or definitive diagnosis by emergency surgery if that preceded consultant review. Final

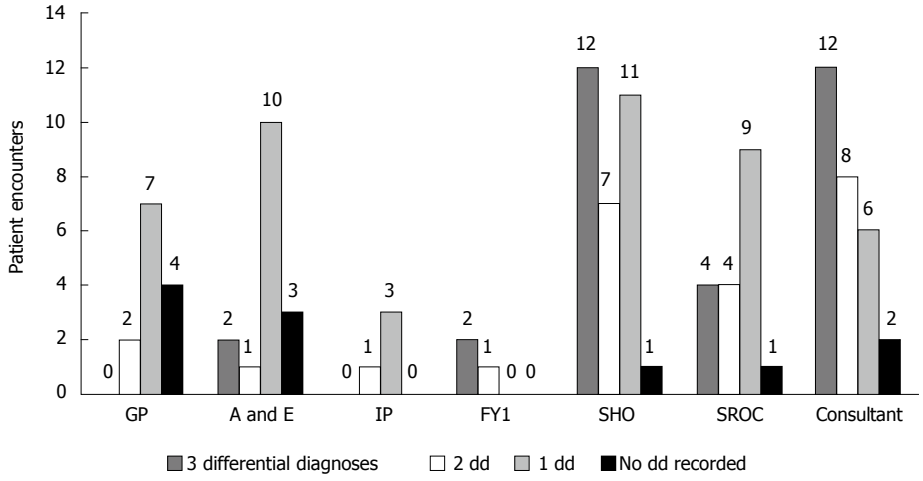

Figure 1 Number of differential diagnoses listed by each doctor grade per patient encounter. Referring physicians (GP, A and E, and IP) rarely recorded more than one differential diagnosis. Among the surgical team, three differential diagnoses were listed most frequently, with the exception of SROC. GP: General practitioner; IP: In-patient referrer; FY1: Foundation year-1; SHO: Senior house officer; SROC: Surgical registrar on-call.

diagnosis was determined by surgical findings, radiological confirmation, or clinical consensus of the rounding on call surgical team comprised of surgical F1, surgical SHO, SROC and surgical consultant as recorded in the discharge summary. All data was kept together in a ring binder and later entered into a spreadsheet for analysis. Authors collected data independently and later on the discrepancies were removed with mutual discussions. There was high and statistically satisfactory inter-observer agreement based upon the Kappa Statistic Score of 0.93.

Data analysis

Data was organized and analyzed using Microsoft Excel® spread sheet (Office 2010, Microsoft Corporation, New York, United States). Statistical analysis was performed with Review Manager 5.2. Each differential diagnosis listed in a doctor/patient encounter was compared to the final diagnosis and scored as correct or incorrect. Failure to list any differential diagnosis was regarded as incorrect.

Endpoints

Recording a differential diagnosis that corresponded with the discharge summary was accepted as an accurate diagnosis.

RESULTS

Patient demographics

Forty-one patients (23 males) with mean age of 61.05 (± 23.24) years were evaluated over 111 patient-doctor encounters. Surgery or other invasive diagnostic procedure was performed in 48.8% of patients. Correct diagnosis was achieved in 85.4% of patients along the primary diagnostic pathway.

Diagnostic outcomes

As shown in Figure 1, FY1, Consultant, and SHO recorded 3 differential diagnoses most often, (67%, 43%, and 39%, respectively) while referring physicians rarely recorded 3 differentials, *i.e.*, 0%, 12.5%, and 0% for GP, A/E, and IP respectively. Consultant was most likely to record a correct diagnosis (75%), followed by SHO (61.3%) and SROC (61.1%) (Figure 2). The accuracy of encounters with 3 differentials listed was 68.75% *vs* 63.77% for just 1-2 differentials. Among the surgical team, the use of 3 differential diagnoses did improve diagnostic accuracy by 8.1%, (65.2% to 73.3%) though significance was not reached (Figure 3). Three differentials were listed at least one time in 23 of the 41 patients. A correct diagnosis was made in 19 of these patients (82.6%). In the remaining 18 patients only 1-2 differentials were ever listed. A correct diagnosis was made in 16 of these patients (88.9%). Of the 32 times in which 3 differentials were listed, only one (3.1%) of these had the correct diagnosis as the third differential (Figure 4).

Contribution in the accurate diagnosis

It is important to identify where diagnoses were made, rather than simply repeated from a previous clinician. If a correct diagnosis had not been made previously, the clinician had the potential to contribute a correct diagnosis. As shown in Figure 5, the surgical SHO contributed the correct diagnoses most often (57.1% of potential contributions). The surgical SHO also contributed 34.3% of all correct diagnoses, the highest of any surgical personnel on call. Three differentials were used to make contributions most often by SHO, followed by Consultant and then by the SROC (66.7%, 60%, and 50% respectively).

Right-to-wrong changes

Failure to include a correct diagnosis made by a previous clinician was regarded as a right-to-wrong change. This occurred 5 times in 111 (4.5%), however 4 of these cases were due to no diagnosis being recorded after a correct

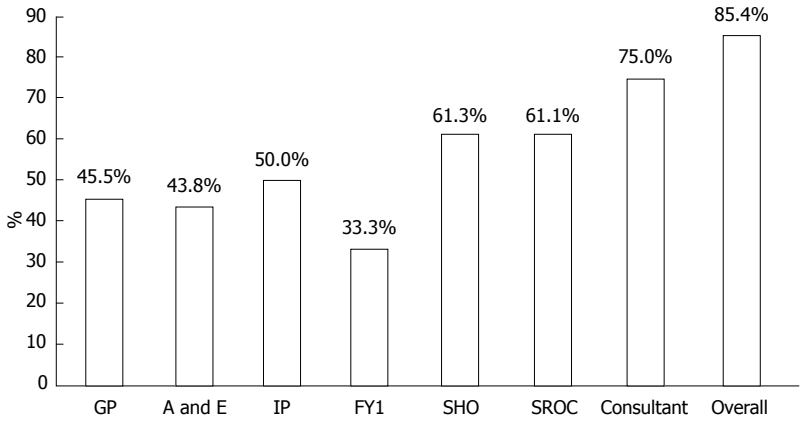

Figure 2 Percentage of patient encounters with a correct diagnosis. Consultant was most likely to record a correct diagnosis, followed by SHO and SROC. Overall 85.4% of patients received a correct diagnosis along the primary diagnostic pathway. GP: General practitioner; IP: In-patient referrer; FY1: Foundation year-1; SHO: Senior house officer; SROC: Surgical registrar on-call.

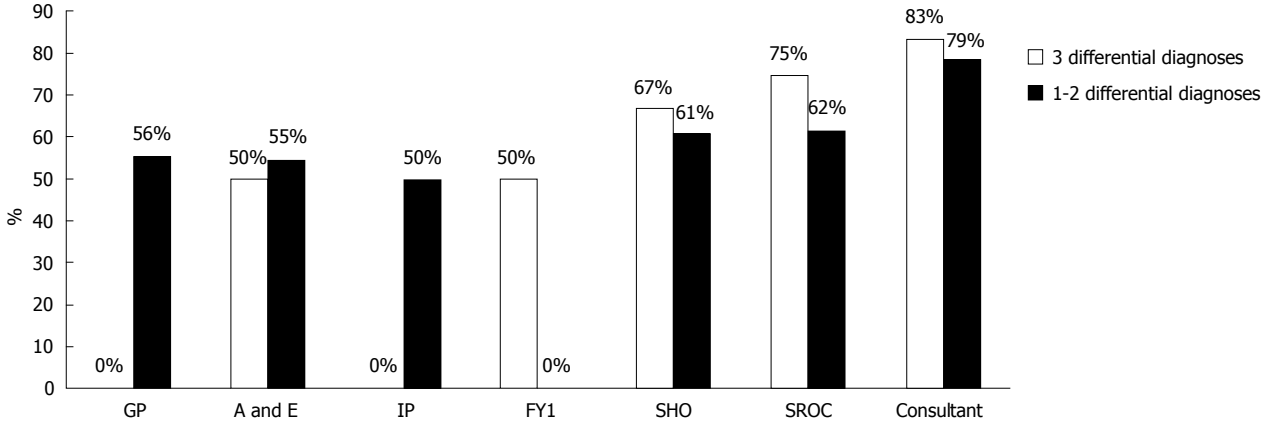

Figure 3 Percentage of correct diagnoses made with 3 differential diagnoses *vs* 1-2 differential diagnoses. The use of 3 differential diagnoses among the surgical team (FY1, SHO, SROC, and Consultant) improved diagnostic accuracy by 8.1% (73.3% *vs* 65.2%). Referring physicians did not follow this trend. GP: General practitioner; IP: In-patient referrer; FY1: Foundation year-1; SHO: Senior house officer; SROC: Surgical registrar on-call.

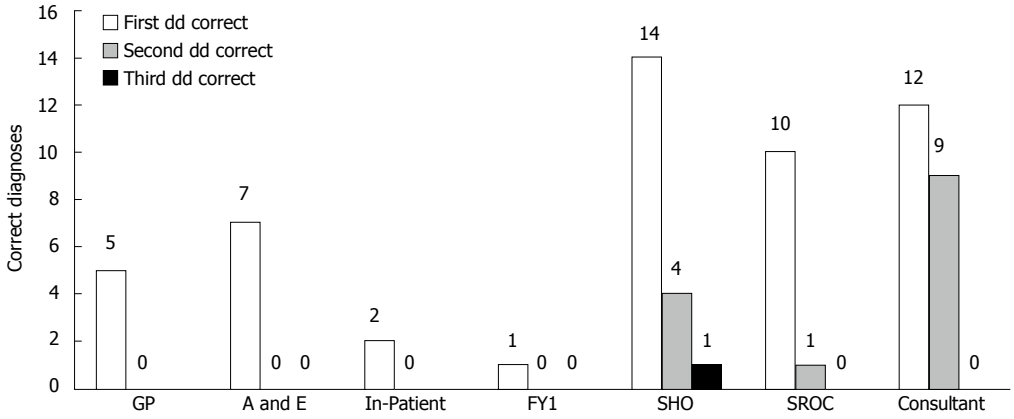

Figure 4 Differential ranking of correct diagnoses by each doctor grade. The correct diagnosis was the first differential listed in most cases for all doctors. Consultant made the correct diagnosis with the second differential diagnosis more than any other group (42.9%), followed by SHO (21.1%) and SROC (9.1%). The correct diagnosis was made with the third differential diagnosis only once, by SHO. (3.1% of 32 times three differentials were listed). GP: General practitioner; FY1: Foundation year-1; SHO: Senior house officer; SROC: Surgical registrar on-call.

diagnosis had been made previously. Only one truly right-to-wrong diagnosis was made, (0.9%) in which malignancy was removed from the list of differentials.

Surgical treatments

Patients referred by a GP were more than twice as likely to undergo surgery as patients referred from A/E. (OR 4.40, CI: 1.09-17.72, $P = 0.04$) However, due to the small size of this study, significance was not reached for GP *vs* in-patient referrals ($P = 0.15$) (Figure 6).

DISCUSSION

Approximately 85% of acute surgical patients can be di-

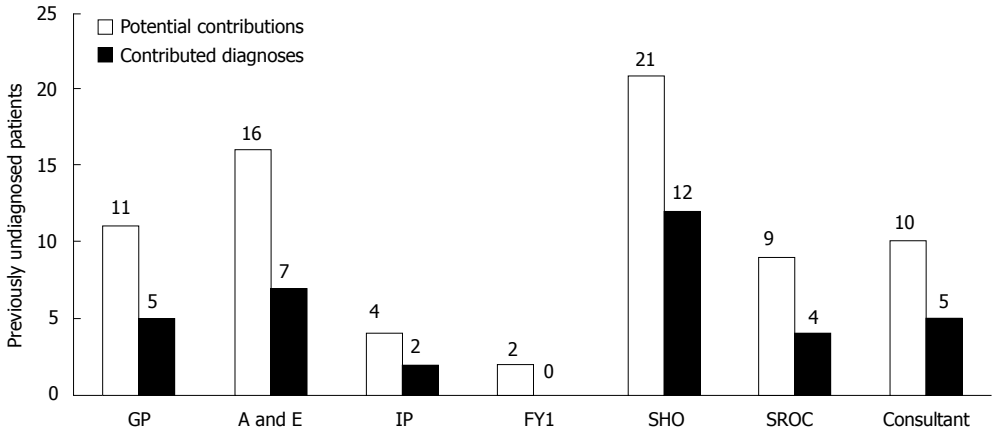

Figure 5 Potential contributions and contributed diagnoses made by each doctor grade. Potential contributions are encounters with patients that had not received a correct diagnosis from a previous physician. SHO contributed the most correct diagnoses and had the highest percent contribution (57.1%) of any group. GP: General practitioner; IP: In-patient referrer; FY1: Foundation year-1; SHO: Senior house officer; SROC: Surgical registrar on-call.

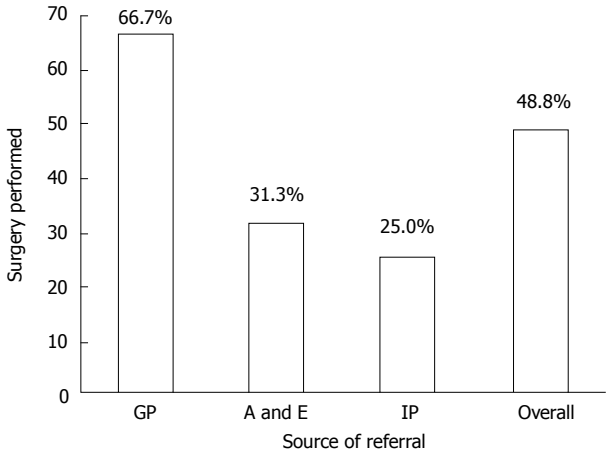

Figure 6 Percentage of patients receiving surgery or other invasive diagnostic procedure by source of referral. GP referrals were more than twice as likely to undergo surgery than patients referred from A and E (OR 4.40, CI: 1.09-17.72, $P = 0.04$). However, due to the small number of in-patient referrals, significance was not reached for GP *vs* In-Patient referrals ($P = 0.15$). IP: In-patient referrer; GP: General practitioner.

agnosed accurately along the primary diagnostic pathway during acute presentations. The surgical consultant was more likely to make a correct surgical diagnosis compared to all health personnel; however it is the surgical SHO that contributes the most correct diagnoses along the diagnostic pathway. Patients referred by a GP are more likely to require surgery as compared to other referral sources.

Premature closure, the cognitive error of failing to continue to consider reasonable alternatives after an initial diagnosis has been made, is often cited as the most common cognitive factor leading to a diagnostic error[7-11]. Much of the focus on decreasing cognitive errors has been on improving clinical reasoning and decision-making by educating physicians about how they make decisions and teaching the use of de-biasing techniques and active meta-cognitive review[12]. Some difficulties with the implementation of these strategies include time, cost, and physician interest, as well as the need to prove the efficacy of these strategies in clinical practice[13]. The potential to reduce the incidence of premature closure with a simple practice that would require no further training and could be easily tested in clinical practice would be ideal as a means to reduce dangerous and costly diagnostic errors. The authors suggest that the practice of clearly listing 3 differential diagnoses in the patient notes is a simple way to modestly decrease the cognitive error of premature closure. Listing of three differentials *vs* listing of one or two differentials seems to improve the diagnostic accuracy among the surgical team, although a larger study would be needed to reach statistical significance. For the 8.1% improvement in diagnostic accuracy seen among the surgical team to be statistically significant (95%CI, 80% power), over 547 patient records should be evaluated. Further support for the use of three differentials comes from the increased proportion of diagnoses contributed using this method. Given the impact of misdiagnosis on the healthcare system, the difficult nature of reducing cognitive errors in clinical practice, and the simplicity of the intervention described, the authors feel it is worthwhile to consider further study in this area to explore any benefit of this practice.

Limitations

The small size of this study limits the statistical significance of many of the trends seen in the data. Other limitations noted during the data collection included difficulty in locating GP referral letters in the patient notes and therefore not including those encounters, as well as missing patients that were seen by on-call surgeons in the evening and subsequently discharged before morning rounds. The use of a junior doctor scribe when patients are reviewed by a consultant or registrar may result in differential diagnoses being stated but not recorded, and therefore not counted.

Future implications

One of the strategies to reduce diagnostic error is to de-

velop pathways for feedback[2,14]. It is particularly important to develop feedback pathways for the junior doctors, as it has been shown that less experienced doctors tend to most over-estimate their diagnostic accuracy[2]. With anonymity removed, the basic design of this study seems well suited to enable feedback to each physician involved in the care of an acute surgical patient. In this way a simple score could be reported as a way to objectively evaluate diagnostic performance, with the ultimate goal of self-improvement and future decrease in diagnostic errors. This approach would allow feedback not just after a negative event, as is the case with many feedback systems in place, but would track performance in a simple, ongoing manner.

COMMENTS

Background

Accurate clinical diagnosis in acutely admitted surgical patients is of immense importance because of the necessity of timely surgical interventions such as need of laparotomy, laparoscopy and or organ resection. Inaccurate diagnosis can lead to serious consequences in terms of delayed treatment, prolonged hospital stay, increased operative morbidity or mortality putting excessive strain on the health resources. Any measure which directly or indirectly may influence the diagnostic accuracy in acute surgical patients should be investigated and implemented in a timely manner to avoid these consequences. This article highlights the value and shortcomings of a referral pathway through which acute surgical patients pass through and get accurately diagnosed for the optimum management.

Research frontier

Various studies published on this topic, although reported the diagnostic accuracy of different grades of acute surgical team with variable accuracy. This is the first study which investigates the diagnostic accuracy of all sources of referral during the course of management of acutely ill patients such as general practitioners, A/E doctors, surgical juniors, surgical middle grade doctors and eventually surgical consultant on call.

Innovations and breakthroughs

The potential to reduce the incidence of mis-diagnosis with a simple practice that would require no further training and could be easily tested in clinical practice would be ideal as a means to reduce dangerous and costly diagnostic errors. The authors suggest that the practice of clearly listing 3 differential diagnoses in the patient notes is a simple way to modestly decrease the cognitive error of premature closure. Listing of three differentials *vs* listing of one or two differentials seems to improve the diagnostic accuracy among the surgical team, although a larger study would be needed to reach statistical significance. For the 8.1% improvement in diagnostic accuracy seen among the surgical team to be statistically significant (95%CI, 80% power), over 547 patient records should be evaluated. Further support for the use of three differentials comes from the increased proportion of diagnoses contributed using this method. Given the impact of misdiagnosis on the healthcare system, the difficult nature of reducing cognitive errors in clinical practice, and the simplicity of the intervention described, the authors feel it is worthwhile to consider further study in this area to explore any benefit of this practice.

Applications

One of the strategies to reduce diagnostic error is to develop pathways for feedback. It is particularly important to develop feedback pathways for the junior doctors, as it has been shown that less experienced doctors tend to most over-estimate their diagnostic accuracy. With anonymity removed, the basic design of this study seems well suited to enable feedback to each physician involved in the care of an acute surgical patient. In this way a simple score could be reported as a way to objectively evaluate diagnostic performance, with the ultimate goal of self-improvement and future decrease in diagnostic errors. This approach would allow feedback not just after a negative event, as is the case with many feedback systems in place, but would track performance in a simple, ongoing manner.

Terminology

FY1: It stands for foundation year 1. The group of junior most surgical doctors in the United Kingdom NHS Trust health system which start clinical practice just after finishing medical school. SHO: It stands for Senior House Officer which a surgical grade after finishing two years of foundation training (FY1 and FY2). SROC: Its stands for Surgical Registrar On Call. Surgical registrar is of variable experience depending upon the step of ladder on training pathway (year 1 to year 8).

Peer review

This is an interesting article.

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