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Global Views on Digestive Diseases



Greger Lindberg, MD

Department of Medicine, Division of Gastroenterology & Hepatology, Karolinska Institutet, Stockholm, Sweden
Email: Greger.Lindberg@ki.se



Henry J. Binder, MD

Professor of Medicine and Cellular & Molecular Physiology, Yale University School of Medicine, New Haven, Connecticut, USA
Email: henry.binder@yale.edu

A very striking feature of medicine is that prevalence of diseases varies markedly in different populations around the globe. Multiple factors are responsible for such variability. Only some of the factors responsible for this varied incidence of disease burden have been identified, though most have defied characterization. Not surprisingly, important factors include genetic variability and differences in distribution of infectious agents. The high incidence of chronic pancreatitis in parts of the Indian subcontinent is certainly one example of such differences in a digestive disease; while pockets of very high prevalence of HCV have been identified.

Until recently, Inflammatory Bowel Diseases (IBD) (ulcerative colitis and

Crohn's disease) have been identified primarily in so-called developed countries (See Figure for distribution of IBD throughout the world in the 1980s).

In addition, disease prevalence changes over time. Obviously, an increased standard of living is often associated with reduced infectious diseases, which will result in an altered pattern of digestive diseases. The reduced burden of *H. pylori* has resulted in a marked decrease in the occurrence of duodenal ulcer and some forms of gastric carcinoma. However, over the past fifty years several autoimmune diseases have increased in prevalence and it has been suggested that the reduction or a change in types of enteric pathogens may also have been responsible for such

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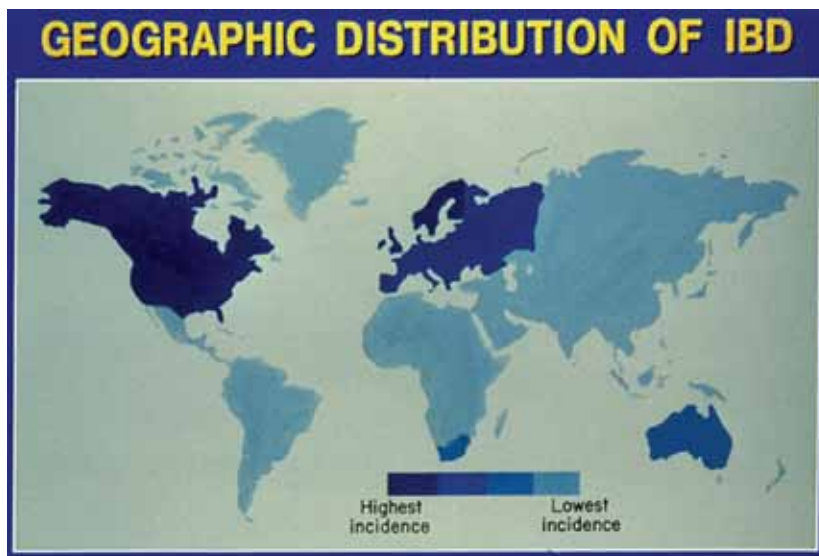
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Email: info@worldgastroenterology.org

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changes. As a consequence, the *hygiene hypothesis* has been proposed as a potential explanation for the increased prevalence of such diverse diseases as asthma, Crohn's disease and possibly celiac disease.

Over the next several months e-World Gastroenterology News (e-WGN) plans to present a series of articles that highlight these differences in disease prevalence both in regard to different populations and as a function of time, i.e., differences that occur over time. In this issue, Dr. David Fleischer and colleagues discuss the high prevalence of carcinoma of the esophagus in specific areas of Asia and Africa, and contrast the characteristics of this carcinoma in high-risk and low-risk areas. We think that a global view of changing disease spectra can help us to understand better causality of gastrointestinal diseases. ■

IBD Research Review

As part of the WGO's campaign to raise awareness about inflammatory bowel disease (IBD) throughout 2010, an IBD expert will be recommending and highlighting a "gold standard" article on IBD, with a direct link to the original source, in each issue of e-WGN this year.



ARTICLE

Chang-Qing Li, Xiang-Jun Xie, Tao Yu, Xiao-Meng Gu, Xiu-Li Zuo, Cheng-Jun Zhou, Wei-Qing Huang, Hua Chen and Yan-Qing Li. Classification of Inflammation Activity in Ulcerative Colitis by Confocal Laser Endomicroscopy. *Am J Gastroenterol* 2010; 105:1391–1396



IBD EXPERT: K L GOH, MD

Head of Gastroenterology and Hepatology, Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia

Dr. Goh's comment on the article: Grading of inflammation activity is important in ulcerative colitis. However, conventional white light colonoscopy evaluation is not reliable. Confocal laser endomicroscopy, where available, is a significant advancement in the endoscopic evaluation of UC. It allows assessment of several features including distortion in crypt architecture, microvascular changes and a newly described observation: fluorescein leakage into the crypts. These alterations correlate well with histological changes and allow a quick, non-invasive and reliable way of assessing the severity of UC in patients

JK Introduction to Dr. Goh: Professor K L Goh - Head of Gastroenterology and Hepatology, Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia, is one of our very respected IBD Review Team members.

He has helped WGO and Professor Charles Bernstein, the Review Team Chair, build the WGO Guideline on IBD. His experiences in the field - his impressive list of more than 100 publications in this and related fields and especially his awareness of racial and ethnic issues when studying IBD have been very helpful indeed.

It is particularly welcoming that his selection provides a window on Chinese research.

The WGO IBD guideline is also available in Mandarin:
<http://www.worldgastroenterology.org/inflammatory-bowel-disease.html> ■

Oral and Pharyngeal Cancer



René Lambert, MD

I.A.R.C., Lyon, France
E-mail: lambert@iarc.fr

INTRODUCTION

Head and neck cancers originate in lips, oral cavity, nasopharynx, oropharynx, hypopharynx and larynx. The Oral cavity includes the mucosal lining of the lips, the buccal mucosa, the retromolar trigone, the alveolar ridges, the anterior two-thirds of the tongue, the floor of the mouth and the hard palate. The Oropharynx includes the posterior third of the tongue, the soft palate and uvula, the tonsils, and the posterior pharyngeal wall. The Hypopharynx, which is posterior to the larynx, extends from above the plane of the hyoid bone to the plane of the inferior border of the cricoid cartilage, below, and includes 3 zones: the pyriform sinuses, the posterior pharyngeal wall and the post-cricoid area. Superficial carcinoma in the oropharynx may be missed during upper GI endoscopy. Giving attention to this first step of endoscopy should be encouraged, because oropharyngeal cancer is frequent in developing countries. Although several epidemiology studies have worked both on oral and pharyngeal cancer, the subdivisions (C-00 to C-14) in the codes listed in the International Classification of Diseases (ICD -10) is a frequent cause of arbitrary choices and disparities in the literature.

THE BURDEN OF OROPHARYNEAL CANCER

Incidence

Worldwide, over 90% of oropharyngeal tumors are squamous cell carcinomas. In the IARC Globocan database incident cases occurring for both sexes in the oral cavity in 2002 are estimated at 91,150 in more developed countries and at 183,000 in less developed countries. The respective figures for cancer of the pharynx are 48,500 in more developed countries and 81,800 in less developed countries.

In most tumor registries men show a higher risk than women. There are considerable variations between countries in the site of the tumor in oral cavity or pharynx. In the IARC database Cancer Incidence in Five Continents, Vol. IX for period 1998-2002, the observed ASR incidence / 100,000 for cancer of the hypopharynx and mouth is high in certain developing countries (Pakistan, Brazil, India) and also in one developed country (France). In India (Mumbai registry) the respective figures are 4.1 in men and 0.9 in women for hypopharynx (C-12-13), and 6.1 and 3.7 for mouth (C-03-06). In Pakistan (South Karachi registry) the respective figures are 4.6 in men and 1.8 in women for hypopharynx, and 15.3 and 12.3 for

mouth. In France (Manche registry) the respective figures in men and women are 9.8 and 0.3 for hypopharynx, and 7.5 and 0.6 for mouth. In contrast in the white population of the USA (9 SEER registries) the respective figures in men and women are 0.9 and 0.2 for hypopharynx, and 2.1 and 1.2 for mouth.

The most common localization of cancer in the oral cavity is the tongue, except in South East Asia where buccal mucosa accounts for 40% of mouth tumors caused by tobacco chewing. Tumors of the tongue and floor of mouth are more common in Europe and caused by alcohol drinking and cigarette smoking. Tonsillar squamous cell carcinomas are relatively frequent. About 70% of all hypopharyngeal tumors occur in the pyriform sinuses, followed by the posterior pharyngeal wall (about 25%) and the postcricoid area (about 5%). Hypopharyngeal cancer is uncommon in the USA where approximately 2,500 new cases are diagnosed each year. In France, Spain, Slovakia and Slovenia high incidences of oropharyngeal and hypopharyngeal cancers occur in men.

Variations in incidence relate to major causal factors which are alcohol, tobacco smoking, and in South East Asia tobacco and Betel Quid chewing. The role played by the Human Papilloma Virus (predominantly HPV-16) has been confirmed in Western countries but also in South East Asia, where the prevalence of oral cancer associated with HPV-16 positivity in the tumor is 27.7% in central India.

The analysis by Conway of 12 cancer registries in the UK has shown that the incidence increased by 18% in men and 30% in women during the period 1990-1999. For oropharyngeal cancer there are distinct temporal trends for tumors localized at sites potentially related to HPV infection and for tumors localized at other sites. This distinction was confirmed in the SEER registries of the USA for the period 1973-2004, with a decreasing incidence in sites unrelated to HPV infection and an increase in sites related to HPV infection. The same difference occurred in the USA National Program of Cancer Registries (NCPR) in 1998-2008: cancer in the tonsils or at the base of the tongue increased with an annual rate of 3% while cancer at sites unrelated to HPV infection (oral cavity and pharynx) decreased.

Mortality

In 2002 the worldwide number of deaths from oral cavity cancer was estimated in Globocan database at 30,700 for more developed and 96,700 for less developed countries; the estimations for cancer of the pharynx being 24,200 and 59,800. The ASR mortality rate per 100,000 is higher in men than in women. For North America in the same database, the ASR mortality from oral cancer is estimated at 1.4 in men and 0.6 / 100,000 in women; respective figures for pharyngeal cancer being 1.3 and 0.4. Higher figures occur in Eastern Europe, particularly in Hungary, with respective estimations in men and women at 10.8 and 1.8 for oral cancer and at 10.3 and 1.3 for pharyngeal cancer. The ASR mortality /100,000 persons in South Central Asia and

India, is estimated in men and women at 7.0 and 4.6 for oral cancer and at 6.7 and 1.5 for pharyngeal cancer. The high toll for oropharyngeal cancer in this region is contrasting with the lower global incidence of cancer - all sites (except skin) included - with estimations of 78.0 in men and 69.9/100,000 in women. The same figure is much higher in Western and developed countries like North America with estimations at 153.1 in men and 112.1/100,000 in women.

In the USA (SEER registries) the observed ASR mortality / 100,000 persons from oropharyngeal cancer in 2002-2006, is 3.9 in men and 1.5 in women. In Europe, higher figures occur in some countries and mortality from oral cancer increased until 1980. Since this period a study conducted in 27 European countries by Garavello has shown a decrease in Western, but not in Central and Eastern Europe. Figures were high in Hungary, where ASR mortality was evaluated at 20.2 / 100,000 persons in mid 1990. The mortality from oropharyngeal cancer was also analyzed for 38 European countries over the period 1975-2004 in the WHO mortality database. In men, ASR mortality rates rose by 2.1% per year between 1975 and 1984, by 1.0% between 1984 and 1993, and declined by 1.3% between 1993 and 2004, to reach an overall rate of 6.1 / 100,000 persons in 2000-2004. Mortality rates were much lower in women, and rose by 0.9% per year up to 2000, and leveled off to 1.1/100,000 persons in 2000-2004. Persisting rises were observed in Hungary and Slovakia where oropharyngeal cancer mortality essentially reflects drinking patterns and type of alcohol.

Survival

Survival of oropharyngeal cancer is estimated in 47 European registries of the Eurocare 4 study; the 5-year relative survival for patients diagnosed in the period 1995-99 is 49.8% for oral cavity, 41.5% for oropharynx, 25.5% for hypopharynx. In Asia, the 5-year survival for oral cavity cancer varied from 23% in India to 67% in China, as recently published in *Lancet Oncology*. The temporal trend in survival from oropharyngeal cancer in North America was analyzed by Gupta in the Ontario Cancer Registry and in the SEER registry: there were no significant changes between the periods 1984-86 and 1999-01 in the incidence of cancer of the oropharynx, while the 5-year relative survival increased from 31.1% to 56.6% in Ontario and from 35.3% to 51% in the SEER registries. The temporal variation in survival, relates to the presence of HPV positive lesions with a better prognosis.

CAUSAL FACTORS

Tobacco smoking or chewing

In the USA, smoking is a major risk factor. For oropharyngeal cancer, heavy tobacco users have a 5 to 25-fold increase in risk. In India, the odds ratio for oral cancer in tobacco chewers are at 3.1. The Trivandrum Oral Cancer Screening (TOCS trial) is an on-going cluster randomized trial implemented in Kerala since 1996 to evaluate the efficacy of oral visual inspection on the incidence and mortality from oral cancer; the trial confirmed tobacco chewing as the strongest risk factor for oral cancer in India (see *Lancet* 2005).

Betel Quid, a chewed mixture of areca nut, slaked lime, spices in a betel

leaf is a risk factor. Tobacco chewed with Betel Quid increases the risk of oral cancer in the ratio of 8 to 15, while Betel Quid alone increases the risk in the ratio of 1 to 4. All forms of areca nut available for chewing cause oral submucous fibrosis, a premalignant lesion. The carcinogenic effect of chewing is linked to specific nitrosamines and alkaloids in the areca nut. Pan-masala is similar to Betel Quid but the ingredients vary widely: fennel seeds, cinnamon, lime, menthol, areca nuts, betel nuts and chemical colored products. In South East Asia, Taiwan and New Guinea, chewing of Betel Quid, with or without tobacco, is also a major risk factor for oral cancer.

Alcohol drinking

Alcohol is a risk factor for oropharyngeal cancer and may act as a solvent, enhancing penetration of carcinogens in target tissues. In the USA alcohol is often combined with smoking. In India the TOCS trial confirms that the risk of cancer in the oral cavity increases by 49% among alcohol drinkers. Overall, alcohol drinking and tobacco chewing are acknowledged as causal factors of oropharyngeal cancer in 75% of cases in this region of Asia.

Human papilloma virus:

Squamous cell carcinomas in the oral cavity or in the oropharynx, are often (around 50%) found positive for Human Papilloma Virus. The most common oncogenic type is HPV-16. Sites related to HPV infection are the base of the tongue and the tonsils. Hybridization identifies 35% of *in situ* tonsillar carcinomas as HPV positive. Sites unrelated to HPV infection are the distal tongue and the floor of mouth. The incidence of oropharyngeal cancer in non smok-

ers and non drinkers rises worldwide; an association is suggested with the prevalence of HPV-16 infection and the changing sexual behavior of young generations with multiple partners and oral sex. In all countries, HPV positive tumors have a better prognosis than HPV-negative tumors. In the USA, an analysis of 9 SEER registries for the period 1973-2004 conducted by Chaturvedi has shown that the incidence of oral squamous cell carcinoma increased in the sites potentially linked to HPV infection with an annual percent change at +0.80, while it decreased in the sites of the oral cavity unrelated to HPV infection. In India various observations confirmed the association between HPV infection and oral cancer; the overall prevalence of HPV-16 in oral squamous cell carcinoma is in the range of 20 to 50%.

HIV/ AIDS

The possible contribution of HIV infection to the increased incidence of oropharyngeal cancer is unclear. Persons with HIV / AIDS are at increased risk (about 2- to 6-fold) for oropharyngeal cancer. In the USA, the relationship between HIV immunosuppression and cancer was explored in 499,230 individuals diagnosed with AIDS, across three periods (1980-89, 1990-95, and 1996-2004). Among persons with AIDS, a statistically significant elevated risk of HPV-associated oropharyngeal cancer was observed. The increase in the risk of oro-pharyngeal cancer with severity of AIDS-related immunosuppression is consistent with some role of HIV infection. Other viruses causing immunodepression may also play a role; this applies to Epstein-Barr Virus (EBV) which is strongly linked to

several human malignancies. EBV-positive oral tumors are located more frequently in the lateral tongue.

Socioeconomic status and nutritional deficiencies

Warnakulasuriya analyzed 41 different studies to confirm a higher risk of oral cancer in persons with a low socioeconomic status: the odds ratio for oral cancer is 1.85 for low education and 2.41 for low income. Differences in causal factors are linked to the socioeconomic status. In India, tobacco chewing is popular in elderly persons and those having a low socioeconomic status. In Northern Europe, an increased risk of cancer in the post-cricoid part of the hypopharynx occurred in women suffering from sideropenic anemia in the Plummer-Vinson syndrome and the recent decrease in the incidence of hypopharyngeal cancer in women in Sweden is related to the diminished prevalence of Plummer-Vinson syndrome.

Heredity

A hereditary factor makes some persons more susceptible to oral cancer; a family history of head and neck cancer is a risk factor in case-control studies. No specific gene has been identified, but genetic alterations in specific enzymes (GSTP1, GSTT1) caused by smoking may influence oral malignancy risk. In synthesis, differences in sex (cancer more frequent in males) or in ethnicity (cancer more severe in blacks) relate to life style rather than to heredity.

Premalignant lesions and carcinogenesis

The molecular steps leading to malignancy in the squamous epithelium have been studied with genomic and

proteomics. Observed alterations include: amplification and overexpression of oncogenes myc, erbB2, cyclin D1 - increased expression of cytokeratin 8 (K8) - hypermethylation leading to p16 and p53 tumor genes inactivation - loss of heterozygosity of the p53 allele - over expression of EGFR and TGF (transforming growth factor) - deregulation of apoptosis, confirmed by the Ki67 immunostaining.

Premalignant lesions of the oropharynx and pharynx include chronic non-healing painful ulcers and non ulcerated areas such as white leukoplakia, red erythroplakia and red and white erythroleukoplakia. Overall, 15 to 20% of these lesions progress to carcinoma. Features associated with risk of malignant progression include - red color - granular or verrucous surface texture - location in the floor of the mouth or the lateral border of the tongue. On histopathology the lesions are graded as low or high grade dysplasia and show DNA instability and allelic losses on chromosome arms 3p, 9p, and 17p.

Generalized fibrosis of the oral soft tissues, called oral submucous fibrosis, results in marked rigidity and trismus caused by the fibroelastic transformation of the juxta-epithelial connective tissues. Fibrosis affects the buccal mucosa, lips, retromolar areas and the soft palate. Occasional involvement of the pharynx and esophagus occurs. In India, this premalignant lesion develops in a large proportion of the users of Tobacco, Betel Quid, or Pan-masala. In this country the prevalence of oral submucous fibrosis is estimated at 4 cases per 1000 adults and as many as 5 million young Indians are suffering from it. In early lesions there is blanching of the mucosa, with a marble-like appear-

ance; histopathology demonstrates a chronic cell infiltration of subepithelial connective tissues containing some eosinophils. Later, there are palpable fibrous bands running vertically in the buccal mucosa or transversally around the mouth opening. The epithelium is atrophic with a reduced vascularity, and dense bundles and sheets of collagen beneath. Oral submucous fibrosis is a precancerous lesion, and a fourth of the biopsied cases demonstrates epithelial dysplasia in addition to the subepithelial alterations.

Diagnosis

The early diagnosis of premalignant lesions in the oral cavity is often conducted by a dentist or stomatologist, after a careful visual exploration completed by vital staining with toluidine blue. Autofluorescence imaging (AFI) with a videoendoscope can improve the detection. In a study of superficial pharyngeal neoplasia, the detection of superficial neoplasia in the pharynx was more performant in AFI (75% of lesions detected), than in white light (33% of lesions detected). Oral cytology is a simple, non-aggressive procedure adapted to confirmation of the diagnosis; oral cells for exfoliative cytology are obtained either by brush cytology or by liquid based cytology. Complementary analyses include cytomorphometry; and identification of markers like epigenetic hypermethylation of p16, MGMT genes, DNA amplification by polymerase chain reaction (PCR) and loss of heterozygosity at p53 sequence. HPV infection can only be detected by DNA-based tests. The most reliable tests are the PCR assay or specific primer and the Hybrid Capture 2 microtiter assay (Digene). The histopathologic analysis



Figure 1: Erythroplakia in the right side of the hard palate; the irregular surface in the antero-lateral part suggests a premalignant lesion. (from IARC Screening Group)



Figure 2: Carcinoma in the lower labial mucosa: chronic ulcer with raised margins. (from IARC Screening Group)

requires a more invasive procedure, the forceps biopsy. When malignancy of the lesion is confirmed, staging of the tumor by the CT-scan can be completed by MRI and PET scan.

Screening and Prevention

Symptomatic patients present non healing sores and pain in the oral cavity; other complaints like odynophagia, otalgia or dysphagia occur when the lesion is located in the hypopharynx. Screening asymptomatic subjects, particularly those who use tobacco or alcohol or both, with visual inspection of the oral cavity and oropharynx, applies to detection of preclinical invasive cancers and precancerous lesions. Visual screening is a simple, affordable, feasible, acceptable and accurate method for early detection of oral lesions; and general practitioners, nurses and allied health workers can be rapidly trained to visual screening. The efficacy of oral visual screening in reducing oral cancer mortality was demonstrated in the large randomized controlled TOCS trial in India (Kerala) involving around 200,000 subjects: a 34% reduction in oral cancer mortality was demonstrated among users of tobacco or alcohol, or both, after three rounds of visual screening provided by health workers at three year intervals (see Lancet 2005). Careful oral and oropharyngeal visual inspection may also lead to early clinical detection of cancers in persons complaining of non-healing ulcers, long standing painful sores, odynophagia, otalgia and dysphagia.

Oropharyngeal cancer is highly preventable by control of environmental risk factors linked to life-style. In Western countries prevention aims directly at those persons who smoke

and drink alcohol in excess. However, the lower risk of oropharyngeal cancer in non smokers and non drinkers is offset by the increased incidence of HPV-16 related cancer of the oropharynx. In South-East Asia prevention addresses to the general population through education about the consequences of chewing tobacco and Betel Quid. The preventive impact of a diet rich in fruit and vegetables, and containing vitamins A and C, on cancer of the mouth, pharynx and hypopharynx has been demonstrated: a metanalysis of 16 case-control or cohort studies, conducted either on men, women or both sexes reported a reduction in the risk of 49% with fruit and 50% with vegetables. ■

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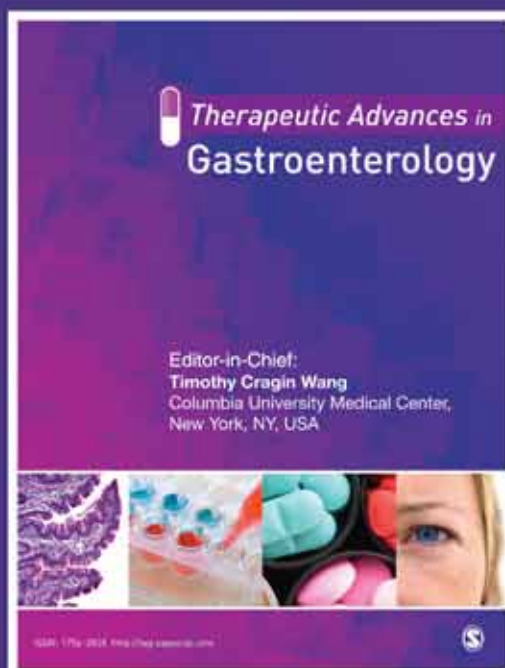
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 SAGE

Geographical Variation in Esophageal Cancer

David E. Fleischer, MD Sanford M. Dawsey, MD

Division of Gastroenterology (D.E.F.), Mayo Clinic, Scottsdale, Arizona and the Division of Cancer Epidemiology & Genetics (S.M.D.), National Cancer Institute, Bethesda, Maryland
E-mail: fleischer.david@mayo.edu

Esophageal cancer (EC) is the 6th leading cause of cancer death worldwide. It is estimated that there were 462,000 new EC cases and 386,000 EC deaths in 2002, only 25,000 fewer deaths than were caused by breast cancer (1). About 80% of EC cases occur in developing countries. In the US, EC is the 9th leading cause of cancer death, with an estimated 16,470 new cases and 14,530 deaths due to EC in 2009 (2).

One striking characteristic of EC throughout the world is its great geographic variation in incidence, with 10-fold differences reported over distances of a few hundred kilometers. Worldwide, the highest risk populations are found in two geographic belts, one in central Asia from the Caspian Sea to north central China, and the other from eastern to southern Africa (Figure 1) (3). Age-adjusted incidence rates over 100 cas-

es/100,000 inhabitants/year have been reported from some areas in these regions (4). Intermediate risk populations are found in southern South America (in southern Brazil, Uruguay, Paraguay and northern Argentina), and in northwestern France. Most of the world is considered low-risk, with incidence rates less than 10/100,000/year. In the SEER cancer registries in the US, the age-adjusted incidence of EC/100,000/year in 2002 – 2006 was 7.9 in white males, 1.9 in white females, 9.3 in black males, and 3.0 in black females (5). In low-risk countries like the US, the male:female ratio of cases is usually about 3-4:1, but in the highest risk populations, this ratio approaches or even falls below 1:1 (4).

Throughout most of the world, and in all high-risk populations, esophageal squamous cell carcinoma (ESCC) is by far the most common histologic type of esophageal cancer. Over the last few decades, however, esophageal adenocarcinoma (EA) has become more common in the low-risk populations of the United States and Europe, likely due to increases in obesity, gastroesophageal reflux and Barrett's esophagus.

The major risk factors for esophageal cancer differ in low-risk and high-risk populations (4) (Table 1). In most low-risk countries, cigarette smoking and alcohol consumption are the dominant risk factors for ESCC. In the US, over 90% of ESCC cases can be attributed to these two exposures alone. Additional contributing risk factors include a low dietary intake of fruits and vegetables and

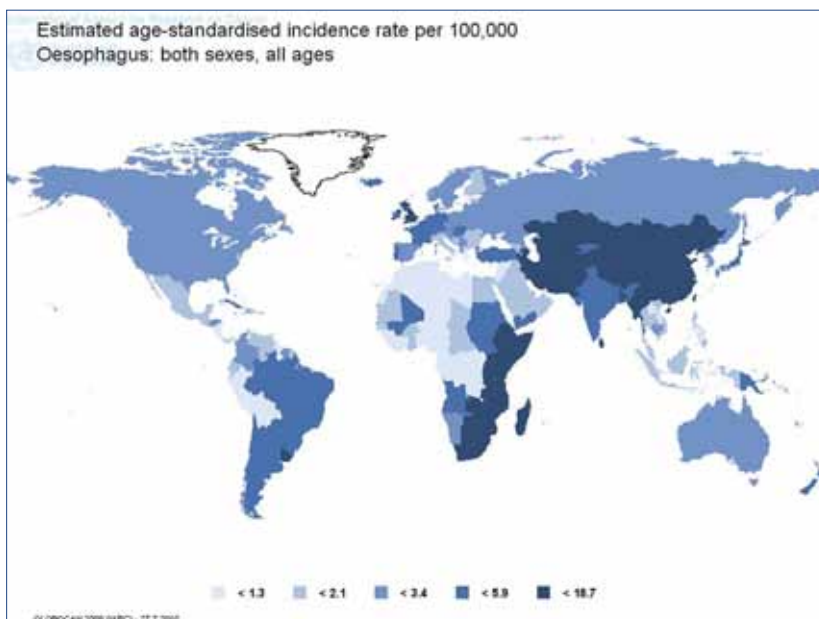


Figure 1. Map displaying incidence rates for esophageal cancer throughout the world

Table 1: Characteristics of Esophageal Cancer in Low-Risk and High-Risk Populations

Characteristic	Low-Risk Populations	High-Risk Populations
Incidence Rate	< 10/10 ⁵ people/year	up to > 100/10 ⁵ people/year
Male:Female Ratio	4:1	1:1
Predominant Histology	Adenocarcinoma (60%)	Squamous Cell Carcinoma (90%)
Risk Factors	Tobacco	Diet low in FAV
	Alcohol	Micronutrient deficiencies (Se, Zn)
	Diet low in FAV	PAH exposure
	Low SES	N-nitroso compounds
	Obesity	Acetaldehyde
	GERD	Hot Drinks
	Barrett's esophagus	Low SES
		Family History
5-year Survival Rate	15%	< 10%

Abbreviations: FAV, fruits and vegetables; Se, selenium; Zn, zinc; SES, socioeconomic status; GERD, gastroesophageal reflux disease

factors related to low socioeconomic status. A few host medical conditions have also been associated with increased risk of ESCC in low-risk populations, including previous or concurrent squamous cell carcinoma of the head and neck region, achalasia, tylosis, caustic esophageal strictures, and the Plummer-Vinson syndrome. The major risk factors for EA are Barrett's esophagus, gastroesophageal reflux, obesity, and cigarette smoking.

In most high-risk populations, tobacco and alcohol are not major risk factors for ESCC. Tobacco consumption in these groups is typically low, both in terms of the prevalence of smoking and in the amount of tobacco consumed by smokers, and alcohol consumption is even lower. In addition, in the highest-risk areas, where there are nearly as many ESCC cases in women as in men, virtually none of the women smoke or drink. These high-risk groups may, however, be exposed to some of the major tobacco carcinogens, such as polycyclic aromatic hydrocarbons (PAHs),

nitrosamines and acetaldehyde, in other ways. Recent studies have documented high levels of PAH exposure in nonsmokers in Linxian (a county in the high-risk region in north central China), in northeastern Iran and in southern Brazil. The source of these exposures is not yet known, although in Linxian it may be related to ingestion of ambient soot particles released from heating and cooking with soft coal in unvented stoves, while in Brazil it may be caused by drinking the beverage mate. Non-tobacco exposure to nitrosamines and acetaldehyde has also been suggested in Linxian and in northeastern Iran, possibly due to changes in oral bacteria that accompany poor oral hygiene and tooth loss. Other risk factors reported in high-risk areas include diets low in fruits and vegetables, low levels of certain micronutrients, especially selenium and zinc, low socioeconomic status, exposure to fungal toxins such as fumonisins, and drinking hot liquids.

One of the most consistent risk factors for ESCC in high-risk popula-

tions is family history, and preliminary molecular studies support a role for genetic susceptibility in the etiology of ESCC in these areas. Studies have shown high frequencies of loss of heterozygosity (LOH), characteristic patterns of gene expression, and significant differences in both LOH and gene expression by family history in tumors from north central China. In addition, recent genome-wide association studies have identified several susceptibility loci in this high-risk population.

Both cell types of esophageal cancer have a dismal prognosis. In the most recent SEER data, for 1999 – 2005, the overall 5-year relative (disease-specific) survival for EC patients was 16.4% (5). This has improved from 4.7% in 1975 – 1979, but it is still the third lowest survival rate (after pancreas and liver) among major cancers. In developing countries, the 5-year survival rates are usually less than 10%.

The main reason for poor survival in esophageal cancer is that most tumors are asymptomatic and go undetected until they have spread beyond the esophageal wall. The esophagus is a distensible organ - it distends to let food pass - so most patients do not complain of dysphagia or other symptoms until the tumor significantly obstructs the lumen, and by that time it has usually invaded through the wall and/or metastasized. Significant reduction in esophageal cancer mortality, both in low-risk and in high-risk populations, will probably require the development of successful new strategies for screening asymptomatic high-risk individuals which can diagnose and treat more cases at earlier, more curable stages of the disease.

We think there are five components needed for a successful early detection and treatment program for esophageal cancer:

1. Identification of the clinically important precursor lesions, which will be the targets for screening and treatment.
2. Accurate, cost-effective primary screening tests that can detect precursor and early invasive lesions and are acceptable to asymptomatic high-risk individuals.
3. Reliable techniques for endoscopic localization of precursor and early invasive lesions, to permit accurate targeting for diagnostic biopsies and focal therapy.
4. Reliable techniques for accurate staging of early invasive lesions, to allow the triage of patients to the most appropriate treatment.
5. A spectrum of curative therapies for precursor and early invasive lesions that are acceptable to asymptomatic individuals.

Early detection is the key to less invasive management and improvement in survival for esophageal cancer. A national early detection program for ESCC is now being implemented in high-risk areas of China, and similar early detection programs are being considered in parts of Iran and Kenya.



Figure 2. International team from left to right, Drs Fleischer, Bergman, Wang, Dawsey, and Utley.

An example of an international collaboration which is contributing to the Chinese program is now ongoing in Feiching and Beijing, China under the leadership of Dr. Wang Guiqi (Cancer Hospital, Chinese Academy of Medical Sciences), with co-investigators Dr. Jacques Bergman (Academic Medical Center, Amsterdam); Dr. David Fleischer (Mayo Clinic Arizona); Dr. Sanford Dawsey (National Cancer Institute); and Dr. Bas Weusten (St. Antonius Hospital, Nieuwegein, The Netherlands) (Figure 2). Patients identified with precursor lesions or early squamous cell cancers are being treated with radiofrequency ablation (6). In some cases, endoscopic mucosal resection is also utilized. BARRX, Incorporated, Sunnyvale, California, is supporting this study. ■

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The worldwide success stories of World Digestive Health Day 2010

Every year the WGO raises awareness about a particular digestive disorder through a yearly campaign that in 2010 has focused on Inflammatory Bowel Disease (IBD). This year's efforts culminated in a very successful World Digestive Health Day (WDHD) on May 29, 2010 that inspired WGO member societies in 29 countries to organize over 50 events.

The lighting of the inaugural lamp at the World Digestive Health Day event in Bhubaneswar, India, where an IBD symposium and a general IBD awareness meeting were held. A WDHD event has been organized in Bhubaneswar, India every year since the WDHD campaign was initiated in 2005. WGO is proud to include India on the list of the most active countries to take part in WDHD, with four different events organized in various parts of the country this year.



The Spanish Digestive System Foundation (FEAD) organized an impressive media event in Madrid which resulted in several newspaper articles and TV and Radio transmissions.

A very successful WDHD event took place in Moscow, Russia, where an international conference "Modern Tendencies in IBD Treatment" took place on May 28, 2010. Image: left to right: Prof. I. Khalif, Deputy Director State Scientific Centre of Coloproctology, President of the Russian group of IBD research; Prof. E. Belousova, Vice President of the Russian group of IBD research; Prof. E. Quigley, Past President, World Gastroenterology Organisation; Prof. G. Vorobiev, Director, State Scientific Centre of Coloproctology, President of the Russian Coloproctology Association; Prof. A. Parfenov, Head of the Department Intestinal Disorders of the Central Scientific Research Institute of Gastroenterology.



In Venezuela several events were held all over the country, all of them focusing on education and awareness about IBD. Under the guidance of Dr. Gisela Romero, the Zulia University hosted three lectures and other events for future HCPs about IBD throughout the spring 2010.

Under the patronage of the Ministry of Health in Syria, the Syrian Group for the Study of Inflammatory Bowel Disease (IBD) in collaboration with the Syrian Society of Gastroenterology, organized a WDHD event that highlighted IBD in the region and brought together prestigious experts from all over the country.



UEGW 2010 in Barcelona

Join the 12,000 physicians, researchers and academics from around the world and learn about current research results! Witness the outstanding scientific programme with an emphasis on the newest research advances as well as clinical and technical innovations and take part in educational courses on diagnostic methods and treatment techniques! Exchange ideas with medical experts, patient organisations' representatives and common interest groups and contribute to a meeting whose success is also in your hands!

Scientific Programme Highlights

The **United European Gastroenterology Week (UEGW)** has been organised annually since 1992 and has become the largest and most prestigious GI meeting in Europe.

Highlights for UEGW 2010 Barcelona 2010 will build on the reputation of previous UEGW's as world class clinically-oriented meetings. Particular highlights will include:

- Clinical updates by international experts
- Increased coverage of GI oncology, in response to the evolving role of many gastroenterologists
- A wider range of interactive formats such as debates and keypad voting sessions
- Live endoscopy sessions in both the main programme and the postgraduate course
- Expanded "Case Presentation" sessions, with keypad voting
- Practical hands-on learning, for example for endoscopy and ultrasound

WGO's IBD Symposium

As part of WGO's World Digestive Health Day, a special WGO satellite symposium will be held on 24 October with internationally renowned IBD investigators presenting on nutritional issues in IBD, diagnostic testing in IBD and choosing between surgery and biological therapy in IBD. The work of the WGO Task Force has been made possible by an unrestricted educational grant from Shire, plc. Please see the advertisement on page 19 for more information.

Translational Science

In parallel, the quality and accessibility of the translational science will be improved.

Features will include:

- A major international two-day symposium on GI and liver stem cells organised by Hans Clevers and Tania Roskams which is open to everyone registering for the UEGW.
- Basic science workshops, where specific cutting-edge topics are dissected and discussed.

Original Research

Importantly, the UEGW is becoming the showcase for the best original GI and liver research from Europe and elsewhere. To encourage this, the Scientific Committee is making the oral abstract sessions more prominent and more interactive, and is rejuvenating the poster sessions. Come and see the very latest research. Ask questions to the researchers! Put yourself at the cutting edge!

Postgraduate Course

Finally, the UEGW Postgraduate Course is growing in prestige and size year on year. The Barcelona 2010 Course will include plenary sessions on GI / liver cancer and IBD and parallel courses including live endoscopy, GI oncology for medical and surgical gastroenterologists, hepatology and IBD.

Public Events at UEGW

Since 2007 UEGW has started organising two very successful public events: a Charity Run and a Public Health Day. Organised by the UEGF Public

Affairs Committee, the UEGF Fun Run has become a traditional charity event during the past few years. With 250 participants at UEGW Paris 2007, the number of athletes has risen to approximately 400 at the Fun Run on occasion of UEGW Vienna 2008. The UEGF Public Affairs Committee is pleased that this charity event has become an attractive and highly regarded activity during the annual congress. Delegates of the UEGW 2010 are invited to register for the this year's "**Run Against Colon Cancer**", an interesting 5 km running course starts and finishes close by the congress venue (CCIB).

Members of the public and delegates are further welcome to attend the **Public Health Day 2010** which will be organised on occasion of UEGW Barcelona 2010. Representatives from local patient organisations, Foro Español de Pacientes and Europacolón España as well as world renowned experts will discuss current issues in the field of digestive cancer together with patients.

UEGF hopes that you will join us in Barcelona and contribute to a successful gastroenterology meeting with excellent science and education in the field. ■

Website Links:

www.uegf.org

www.uegw10.uegf.org



A new WGO Training Center was inaugurated in San José, Costa Rica

Richard A. Kozarek, MD

President, World Gastroenterology Organisation
Executive Director, Digestive Disease Institute
Virginia Mason Medical Center
Seattle, WA

The World Gastroenterology Organisation formally inaugurated its 14th Training Center in San Jose, Costa Rica on March 5, 2010. Under the directorship of Herbert Burgess, MD and with the support of Asociacion de Especialistas en Gastroenterologia y Endoscopia Digestiva de Costa Rica, the Sirius Training Center envisions training gastroenterologists from Central and South America in geographically important digestive disorders and advanced endoscopic imaging techniques. This is particularly important in Costa Rica with its exceptionally high incidence of gastric malignancy and the evolving ability to treat many of these malignancies at an early state with either mucosectomy or endoscopic submucosal dissection. This Training Center has been generously supported over the next five years by Fujinon Latin America (FUJIFILM) both with equipment and WGO administrative support.

The inauguration itself and Combined Scientific Program was attended by gastroenterologists from virtually every South and Central American country as well as Mexico, in addition to WGO representatives Henry Cohen, Eamonn Quigley and Richard Kozarek, as well as representatives from FUJIFILM, Latin America and

the General Manager of its Endoscopy Division, Hisashi Kisimoto, Tokyo, Japan. The meeting included an overview of WGO programmatic activities, an overview of GERD 2010, and an update on Helicobacter by Drs. Kozarek, Quigley and Cohen, respectively, and an afternoon Scientific Symposium.

The WGO looks forward to integrating the Sirius Center into our geographically diverse family of Training Centers and following the trainees who attend both short- and long-term courses relative to such outcome parameters as changes in practice patterns, improvement in diagnostic yield, need for less invasive treatment regimens, and ultimately improvement in gastrointestinal health in patients cared for by these trainees.

The WGO Training Centers are located in Bangkok (Thailand), Bogota (Colombia), Cairo (Egypt), Karachi (Pakistan), La Paz (Bolivia), La Plata (Argentina), Mexico City (Mexico), Rabat (Morocco), Ribeirao Preto (Brazil), San José (Costa Rica), Rome (Italy), Santiago (Chile), Soweto (South Africa) and Suva (Fiji).

WGO Training Center Partnership Program

In an effort to further support the WGO Training Centers, the WGO

launched the Training Center Partnership Program placing a call to national and regional GI societies to partner with WGO centers in order to ensure their sustainable future. The ASGE was one of the first societies to answer that call, for which the WGO leadership expresses its deep gratitude.

ASGE Launches Ambassador Program in the WGO Training Center in Cairo, Egypt

In 2009, the American Society for Gastrointestinal Endoscopy (ASGE) introduced a new initiative called the Ambassador Program. This program was developed to export two of the Society's greatest assets, basic and advanced endoscopic medical care as well as training expertise. Ready access to advanced GI care does not exist in developing countries. Likewise, the education and training of physicians in underserved countries provides a tremendous opportunity for ASGE to leave a lasting mark in these areas. The ultimate goal of the program is to decrease illness and deaths in underserved populations from untreated digestive disorders.

ASGE launched its first Ambassador program in February of this year in Cairo, Egypt. Five highly-skilled ASGE physician members volunteered their time and expertise to train and mentor 10 trainees for a week at the Cairo Training Center (CTC). This Center is located within the Theodor Bilharz Research Institute and is accredited by the World Gastroenterology Organisation. Through the generosity of the WGO, ASGE was

able to utilize this outstanding facility for its program.

The one-week program covered numerous topics related to upper GI bleeding – one of the most common gastrointestinal afflictions facing developing nations in Africa today. The training consisted of didactic sessions as well as hands-on training where physicians and trainees treated patients in need.


This program would not be possible without the grant funding and equipment provided by our industry partners – Pentax Medical Systems, US

Endoscopy and AstraZeneca Foundation. ASGE leadership acknowledges the WGO and expresses its deepest thanks for WGO's generosity in providing the Cairo Training Center for the inaugural Ambassador Program.

For more information on the ASGE Cairo program, becoming an Ambassador or to contribute to future programs visit www.asge.org/ambassador.aspx.



For more information on Cairo Training Center activities, Please contact info@egyptgastrohep.com. ■

Are You Attending WGO's IBD Symposium at UEGW Barcelona?



World Gastroenterology Organisation
Global Guardian of Digestive Health. Serving the World.

Special World Digestive Health Day 2010
IBD Task Force Symposium


IBD: A GLOBAL PROBLEM

Date: Sunday, 24th October, 2010
Time: 16:15-17:45
Venue: CCIB, Room 116

Chairs:
Charles N. Bernstein, MD, FRCPC
 Professor of Medicine, Head, Section of Gastroenterology, Director, IBD Clinical Research Centre, University of Manitoba, Canada
Lloyd Mayer, MD
 Professor and Co-Director of the Immunology Institute, Dorothy and David Merksamer Professor of Medicine, and Professor of Microbiology, Mount Sinai Medical Center, USA

Speakers:
Nutritional issues in IBD - Ernest G. Seidman, MDCM, FRCPC, FACC
 Professor of Medicine & Pediatrics, Canada Research Chair in Immune Mediated Gastrointestinal Disorders, Bruce Kaufman Endowed Chair in IBD at McGill Digestive Lab Research Institute, McGill University Health Center, Montreal General Hospital, Canada
Diagnostic testing in IBD - Geert D'Haens, MD, PhD
 Professor of Medicine, Academic Medical Centre, Section of Gastroenterology, Amsterdam, The Netherlands, Director, Imelda GI Clinical Research Centre, Bonheiden, Belgium
Choosing between surgery and biological therapy in IBD - Iris Dotan, MD
 Head of IBD Service, Department of Gastroenterology and Liver Diseases, Tel-Aviv Sourasky Medical Center, Israel

Inflammatory Bowel Disease (IBD) is a group of inflammatory conditions of the colon and small intestine. The two main types of IBD are Ulcerative Colitis (UC) and Crohn's disease. During 2010 WGO wishes to underscore the emergence and complexities of IBD to doctors in developed and developing countries. Our focus is on optimizing diagnostic approaches and maximizing patient care to enhance the quality of life of IBD patients and to help inform their health care providers worldwide.



The work of the WGO Task Force has been made possible by an unrestricted educational grant from Shire, plc.

SOMAHGEED: WGO member society in Madagascar faced with challenges in GI education and training



Eugene Morel, MD

President, Societe Malgache D' Hepato-Gastro-Enterologie et D' Endoscopie Digestive

SOMAHGEED, the Société Malgache d'Hépatogastro-Entérologie et d'Endoscopie Digestive, is finding ways to confront the challenges of having only three gastroenterologists to meet the needs of the 20 million habitants in Madagascar. "There are some doctors of internal medicine who are specialized in hepatogastroenterology, but this is an insufficient number of GI professionals to provide care for the patients with

digestive disorders in Madagascar and the surrounding regions," comments Dr. Eugene Morel, the President of SOMAHGEED and the only gastroenterologist in the country practicing outside the capital Antananarivo. There are small diagnostic centers of digestive endoscopy, but therapeutic digestive endoscopy hardly exists in Madagascar and even the members of the local GI society often fail to appreciate the need to improve the care

of digestive disorders. "We are looking into creating a training center for digestive endoscopy as well as a training program that would provide local general practitioners, PhD students or doctors of internal medicine with an international degree in digestive endoscopy. As a part of our strategy for the future, there will also be a special congress and an international training course focused on GI training organized in November in Mahajanga," Dr. Morel comments and adds that all external support is welcomed to solve the problem of having such a limited number of trained gastroenterologists in Madagascar. ■

Building the WGO Cascades for Constipation

Constipation[mh]* AND (ethnic groups[mh] OR developing countries[mh])



Justus Krabshuis, MD

Highland Data, Tourtoirac, France
E-mail: justus.krabshuis@highland-data.com

Introduction

If you run a search for articles in Pubmed indexed with the MeSH heading 'Constipation' (constipation [mh]) you get 8614 hits (1).

If you are interested in constipation in ethnic groups or constipation in developing countries (constipation [mh]) and (ethnic groups[mh] or developing countries[mh]) - adopting a more global view - you get 27 hits.

And so, one could say that 'Cascades' serve an unmet need seeing as though the existing constipation literature is almost entirely focused on Western Research in Western settings. So, what is a Cascade and how do we actually build a cascade? Is there such a thing as Cascade based medicine? What relationship – if any – is there to evidence based medicine? Can we search for Cascades in Pubmed? And, crucially, are they useful?

A Cascade is a selection of two or more hierarchical diagnostic or therapeutic options, based on proven medical procedures, methods, tools or products for the same disease, condition or diagnosis, aiming to achieve the same outcome and ranked by available resources.

WGO guidelines try to offer resource-adapted solutions for the diagnosis and management of digestive disorders, and dissemination and implementation of these global cascade based guidelines is one of the organisation's key educational goals.

Lindberg's cascade for the management of constipation

Starting with a thorough search in Medline and Embase for level 1 evidence we build a constipation evidence base. Of course we try to identify the gold standard – it is extremely important but it is the easy part and often – when building the cascade – it

means taking over the relevant parts of an existing guideline from one of the top societies or perhaps a Cochrane review. But usually such gold standards are resource-blind.

In many parts of the world prokinetics (tegaserod, prucalopride) are not readily available. Promoting gold standard options in resource limited settings is not helpful.

Now comes a fascinating if hazardous intellectual journey as the Chair of the guideline review team creates a first draft for the gold standard and lower cascade levels. This is where 'art' and 'science' meet.

The cascade below was designed and built by professor Lindberg, Chair of the WGO Guideline Review team for Constipation. It is intended for patients with chronic constipation without alarm symptoms and little or no suspicion of an evacuation disorder. The main symptoms would be hard stools

Level 1 – limited resources
1. Dietary advice (fibre & fluid) 2. Fibre supplementation 3. Milk of magnesia (Magnesium hydroxide in aqueous solution) 4. Stimulant laxatives (bisacodyl better than senna) for temporary use
Level 2 – medium resources
1. Dietary advice (fibre & fluid) 2. Fibre supplementation, psyllium 3. Milk of magnesia, lactulose, macrogol 4. Stimulant laxatives (bisacodyl better than senna) for temporary use
Level 3 – extensive resources
1. Dietary advice (fibre & fluid) 2. Psyllium or lactulose 3. Macrogol or Lubiprostone 4. Prokinetics (tegaserod, prucalopride) 5. Stimulant laxatives (bisacodyl or sodiumpicosulphate)

1. Search carried out July 12, 2010, 0900 am CET

* [MH] Adding this means we are looking for articles indexed with the Mesh Heading (=indexing term) 'constipation'

Country	Help With Cascades	Country	Help With Cascades
1. Argentina	yes	12. Madagascar	yes
2. Canada	yes	13. Malaysia	yes
3. Croatia	yes	14. Pakistan	yes
4. Denmark	yes	15. Poland	yes
5. Finland	yes	16. Russia	yes
6. Guatemala	yes	17. Slovakia	yes
7. Hong Kong	yes	18. Spain	yes
8. Hungary	yes	19. Sudan	yes
9. India	yes	20. Turkey	yes
10. Iran	yes	21. UAR	yes
11. Jordan	yes		

and/or infrequent bowel motions.

Once we have a draft cascade in place it will then be sent to all of the WGO National Societies of Gastroenterology (NSG) for comment. We ask them: what do you do in your country?

Above is a list of some of the NSGs who responded with recommendations and advice on the Constipation Treatment cascade.

And here is an edited version of what some of the NSGs wrote back to us:

- Macrogol or lubiprostone and prucalopride are not available. Tegaserod has been taken out of market.
- We try to avoid stimulant laxative as Lactulose/lactitol/ macrogol is available.
- Exercise. I avoid lactulose. Adds to the bloating. Micro enema PRN.
- Local suppositories especially glycerin were useful. Locals use herbal treatments-called hulool.
- Would consider larger volume laxatives such as one bottle of magnesium citrate or use of 1-2 L of PEG/GoLyte.
- Adequate fluid intake not mentioned above, dietary management when possible and Mg based products- Milk of Mg or maglalax most practical.
- I do not recommend using tega-

serod, prucalopride, Macrogol or lubiprostone as the first line even in the extensive resource country. These drugs have serious side effects when used regularly and should not be offered to majority of subjects with chronic constipation. They should be reserved for patients with proven prolong transit and severe constipation who are intractable to diet fiber, psyllium, bisakodyl, senna and lactulose.

- Avoiding medication with impact upon constipation such like cough syrup, anticholinergic drugs, etc.
- Teaching local doctors the cascade guidelines for treating constipation.
- The perception of what is a normal bowel movement varies from country to country. In Asia for example, bowel opening of more than once per day is common place and acceptable as normal and may report constipation if it were less than that. Similarly, stool consistency is often soft in South East Asian countries with the high intake of vegetables and spices and a “normal form” or “hard stool may be interpreted as constipation.
- Yes, but we are a “level 3” country (main difference between milk of magnesia and other osmotics is price.

- The staple diet for the average person is rich in fibre, therefore we tend to encourage high intake of fluid. Bulk-forming laxatives in the form of sterculia (Normacol) as well as osmotic and stimulant laxatives are readily available and somewhat affordable.

Once we have edited and incorporated the feedback from the NSGs – and this is a vital part of our Cascade production system – this is ‘bottom up’ data, this is not armchair or ‘salon’ gastroenterology – we invite comments from the Constipation review team and the Chair of the Guidelines Committee. Now the Cascade is ready and we request the final green light from the Chair of the Review Team (Greger Lindberg) and the Chair of the Guidelines Committee (Michael Fried).

In summary then, here is the cascade workflow:

- Cascade Literature search in Embase, Medline, the Cochrane Library and existing Guidelines
- Review team chair to generate gold standard plus lower level cascade options
- Invite comment from National Societies of Gastroenterology
- Invite comment from Regional Cascade Teams to make sure we cover Latin American, Asian and African viewpoints
- Invite comment form Constipation Review team
- Request permission to publish from the chairs of the Constipation Review team and the chair of the WGO Guidelines Committee
- Finalize draft, translate into 5 other languages and publish

And finally, there is this question: are cascades useful? My (entirely personal) view is: If you don't have it, why should we advise it? ■