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President Message

Message from Prof. Benjamin C.Y. Wong, President

Welcome all of you to the second issue of our newsletter in 2011.

The first half of the year of 2011 has been busy for The Hong Kong Society of Gastroenterology organizing our AGM cum Scientific Meeting on 10 March 2011, joint scientific symposia on 19 May 2011 with Hong Kong Society of Biological Psychiatry and on 26 May 2011with Hong Kong Society of Endoscopy Nurses.

On behalf of the Society, I wish to express my sincere thanks to all who have contributed to this Newsletter: Professors Raymond DuBois, K.L. Goh, Philip Quirke, Hans Tillmann, Doctors In Son Leong, Garrett C.L. Ho and Walter W.K Seto for their scientific summaries, Dr. Wai-Mo Hui and Prof. Justin C.Y. Wu for editing this Newsletter; and friends from the pharmaceutical industry for their generous sponsorship and efforts.

I would like to again remind everyone that our 30th anniversary celebration dinner will be held on 9 December 2011. Please mark your diary and come to celebrate together. I look forward to seeing all of you.

From February 2011, the interactive version of our Newsletters has been online http://www.hksge.org/newsletter. I would like to thank the readers who responded to our call for electronic communication. Please contact our secretariat at gastro@hksge.org any time to change or update your preference.

The next newsletter will appear in October 2011. I look forward to your continued support. Thank you.

Scientific Updates

Inflammation and Cancer: Molecular Targets and Opportunities

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It is now clear that long-term use of NSAIDs leads to a 40-50% reduction in risk for colorectal cancer and some other malignancies. How do these "anti-inflammatory" drugs act to reduce cancer risk (1)? NSAIDs effectively target inhibition of prostaglandin synthesis by the cyclooxygenase enzymes (COX-1 and COX-2) (2). Prostaglandins, such as PGE_2, regulate the expression of several downstream effector genes, some of which regulate pro-inflammatory pathways. These bioactive lipids signal via G protein-coupled receptors (GPCRs), which in turn can transactivate growth factor receptors and regulate cell proliferation, migration, angiogenesis and cell survival (3). Prostaglandin E2 (PGE_2) has been shown, in some reports, to directly activate components of the canonical Wnt signaling system (4). Additionally, PGE_2 can transactivate the epidermal growth factor receptor (EGFR) in colorectal carcinoma cells via a c-Src dependent mechanism that regulates cell proliferation and migration (3). The pathway which regulates degradation of prostaglandins, namely 15-PGDH, is also regulated by EGFR signaling (5,6). We also found that PGDH (as well as certain prostaglandin transporters) may serve as a tumor suppressors in colorectal cancer and provide a possible COX-2-independent way to target PGE_2 to inhibit cancer progression (7). Several large clinical trials have been completed demonstrating that selective COX-2 inhibitors are effective in preventing adenoma regression and prolonging survival in humans with colorectal cancer (8).

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ASIA AT THE CROSSROADS - CHANGING EPIDEMIOLOGY OF GASTROINTESINAL DISEASES IN ASIA

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Introduction

Asia, once the centre of world civilization had lagged behind Europe and North America in socio-economic development in the past two millenniums. Beset with wars, natural disasters and political discord, Asia was considered a poor region of the world. The end of World War II marked the beginning of a new era and the emergence of Japan, the gradual stabilization and growth of China and more recently, India has seen a marked increase in affluence and an improvement in living conditions across the whole region. Once again Asia is at the crossroads.

Major changes in disease and health are inevitable with the dramatic socio-economic changes taking place. As more than half the world's population of approximately 4 billion people live in Asia, changes in trends of disease in Asia would therefore impact significantly on the global health burden.

The epidemiology of gastrointestinal disease in Asia is interesting. Broadly diseases associated with poverty have been common: gastric (GCA) and esophageal cancer while diseases associated with a more westernized lifestyle such as colorectal cancer(CRC), gastroesophageal reflux disease (GERD) and inflammatory bowel disease have been less common. Indeed with the change in lifestyle in Asia, changing trends in these diseases have already been observed in Asia. The changing epidemiology of a disease often provides valuable insights as to possible pathogenic mechanisms and the changing epidemiology in Asia allows us this opportunity to make such observations.

Gastric Cancer

GCA remains one of the most important cancers in Asia with the highest incidences reported from Asian countries such as Japan, Korea and China [1]. Although GCA incidences in Asia have also started to decline as in the West, the rate of decline is nowhere near the latter. With an increase in aging population in many countries in Asia such as Japan, the absolute number of patients has in fact increased, placing a continued burden to health services. The marked decline in GCA in the West has been attributed to the introduction of refrigeration in the 1940s, which has resulted in the increase consumption of fresh fruits and vegetables and a decrease intake of preserved foods [2]. GCA has also been closely linked to *H. pylori* and the decrease in GCA must be linked to the decrease in the infection that is now observed throughout the world. The paradox is that the decline in GCA started before the discovery of *H. pylori* and it has been the improvement in living conditions and in personal and community hygiene that has led to a decrease in infection rather than any direct attempts at treating and eradicating of the bacterium. Many unanswered question however remain in the etiology of GCA in Asia. For example, *H. pylori* is high amongst Indians but the incidence of GCA is low- the so-called "Indian enigma" indicating that the etiopathogenesis of GCA is multifactorial with an interaction between host and bacterial virulence factors and environmental factors particularly diet [3]. Much has been discussed about a cancer protective diet of cucurmin containing curries- a staple of Indian diets.

Colorectal Cancer

CRC has long been considered a Western disease. There has however been clear evidence that CRC incidence rates have been increasing in Asians [4]. In the recent Globocan figures of 2002, ASR rates have increased markedly in Japan and Singapore Chinese and reported to be amongst the highest in the world [1]. In several Asian countries, the ASR of colon and rectal cancer has now surpassed that of GCA [1].

This changing epidemiology follows that of the West where CRC had been steadily increasing from 40-50 years ago (and has now reached a plateau and starting to decline!) - a time lag phenomenon. Increased incidence of CRC could be due to better detection and diagnosis of the cancer. With widespread availability of better health care services in Asia, flexible colonoscopy has become more readily available. However, the continuing rise in CRC rates point to a true increase in CRC [5]. The reasons are likely to be similar to that of the West. Rising affluence with an increase in obesity and a decrease in physical activity have been implicated in CRC [6-8]. On the other hand, the adoption of a westernized diet of higher protein and fat content has also been implicated as a cause for the increase in incidence [9,10]. Without question, CRC will be the major GI cancer in Asia in the coming years.

Peptic Ulcer Disease

As with the West, a decrease in the prevalence of peptic ulcer disease has been documented in several studies from the region [11-14]. While the overwhelming majority of patients were diagnosed to have associated *H.pylori* infection, one study from Philippines has noted a steady decline in prevalence of *H.pylori* associated ulcers [13]. Similar findings were noted in another endoscopy based study from Malaysia where both duodenal and gastric ulcer had declined over a 10 year interval with a decrease in proportion of *H.pylori* infection as well [14]. Reports on the prevalence of NSAID use and the increase in NSAID associated ulcers have also been noted [15] but an intriguing group of patients who are both *H.pylori* and NSAID negative.

Gastroesophageal reflux disease

GERD has been considered a rare disease in the East previously [16]. Indeed earlier studies have shown an inordinately low prevalence of reflux esophagitis. Community-based studies have also shown a low prevalence of reflux symptoms. The situation has changed dramatically. More and better studies are now available which have shown prevalence of reflux esophagitis approaching 20% and prevalence of reflux symptoms of up to 10-15%. More severe grades of esophagitis have also been noted although Barrett's esophagus however remains uncommon in Asia [17].

Helicobacter pylori infection

H.pylori underlies several gastrointestinal disorders including GCA and peptic ulcer disease. Reports from Asia have shown a steady decline of *H.pylori* over the years [18-20]. Studies from Japan and Hong Kong have linked the decrease in *H.pylori* prevalence with an increase in GERD [17].

DISCUSSION

The epidemiological changes that have taken place over a relatively short interval of time point to the influence of exogenous factors. Broadly, lifestyle changes to one that is "westernized" have been blamed. What these changes encompass that are relevant to our discussion are dietary changes, improved living conditions and a decrease in physical activity.

A change in diet to one that is rich in fat and protein has been implicated in the rise in incidence of CRC as well as GERD. This process could be brought about directly by the change in diet or through associated problems such as obesity. Dietary change compounded by a decrease in level of physical activity has made obesity the fastest growing problem in the Asian Pacific region [21]. An epidemic of obesity-associated diseases such as "fatty liver" has already been predicted [22].

Paradoxically, dietary change has also meant a change to a "better" diet – one that contains less salt and preservatives. This has been thought to be the single most important factor in the decline in GCA rates. An improvement in living conditions and better personal and community hygiene has also resulted in the rapid decrease in prevalence in *H. pylori* and as a consequence, a decline in the prevalence of associated gastroduodenal disease: peptic ulcer and GCA. A decrease in *H.pylori* infection has resulted in a healthier stomach with an increase in acid producing capacity which will contribute to the increase in GERD [23]. An improvement in hygiene has conversely been implicated in the increase in inflammatory bowel disease in Western populations [24]. This may also be the case in the Asian population where an increase in prevalence has already been observed.

An important demographic factor to consider is the increase in proportion of the elderly population in the Asian Pacific region. Apart from degenerative diseases, cancers including gastrointestinal cancers would increase and patterns of cancer will also change. Higher consumption of non-steroidal anti-inflammatory drugs in the elderly will result in an increase in gastrointestinal ulceration and associated complications particularly gastrointestinal bleeding despite the decrease in *H.pylori* associated ulcers.

Epidemiological changes in disease is inevitable with time. The challenge for everyone is to identify putative factors and implement modifiable or remedial action to prevent the full deleterious effects of such changes.

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Margins and planes of resection in colorectal cancer

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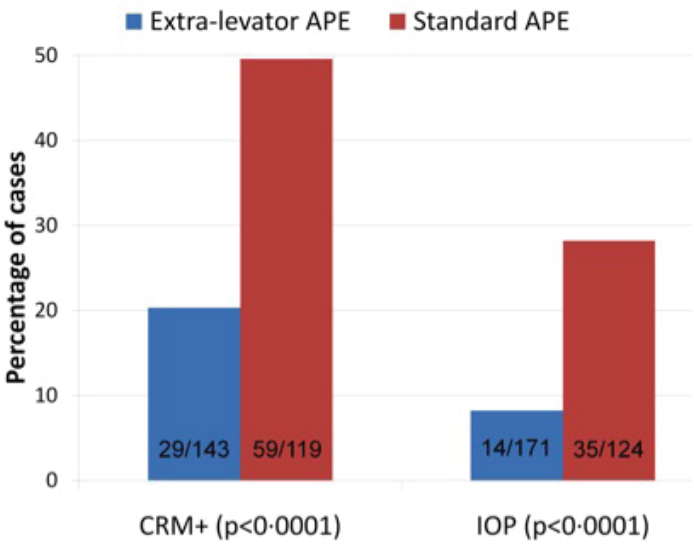
The optimum extent and plane of resection in colorectal cancer surgery is determined by the following goals: retention of the tumour within the specimen, removal of local spread and drainage, and reduction of local recurrence. Excellent surgical technique will lead to less pelvic and intra-abdominal recurrences, improved survival, fewer relapses and more affordable treatment. Current surgical interventions for colorectal cancer include total mesorectal excision, extra-levator excision, and complete mesocolic excision with or without high tie.

Tumour involvement of the distal margin of rectal lesions tends to be minimal at 1% to 2%, while the circumferential resection margin (ie, the area created when the tumour is removed from the pelvis) is involved in 9% to 36% of cases resulting in more frequent local recurrence and poorer survival.[1]

In general, total mesorectal excision for rectal cancer with margin positivity is associated with a better prognosis and fewer recurrences compared with incomplete resection.[2-4] The extra-levator abdominoperineal excision (APE) approach for low rectal cancer, introduced by Dr Torbjorn Holm, has likewise produced superior results in terms of reducing local recurrence, margin positivity, and intraoperative tumour perforation over conventional APE.[5-7]

For colon cancer, complete mesocolic excision with central vascular ligation has been shown to reduce local recurrence and improve overall survival.[8-12] Nevertheless, more effective education and quality control programs for surgeons and photographic audits for pathologists may need to be implemented in order to optimise the prognosis of colorectal cancer.

Figure. Oncological superiority of extra-levator APE for low rectal cancer in Europe



APE, abdominoperineal excision; CRM, circumferential resection margin; IOP, intraoperative perforation

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Achalasia in Hong Kong

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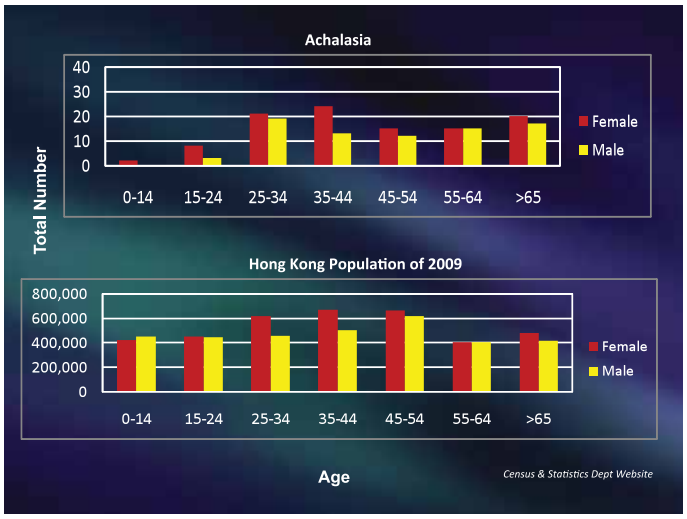
Achalasia is characterized by a loss of peristalsis in the distal esophagus and failure of the lower esophageal sphincter (LES) to relax, thus creating a functional obstruction. Based on the recently concluded 10-year-study by the Hong Kong Society of Gastrointestinal Motility, its estimated annual incidence in Hong Kong is 0.3/100,000 population, which is similar to the annual incidence in Singapore.[1] The mean age at diagnosis is 47.1, while the mean age at onset of symptoms is 45.4. More females than males are diagnosed (ratio: 1:1.33), which Dr Leong attributed partially to the population structure. The three most common presenting symptoms are dysphagia to solid foods, regurgitation, and dysphagia to liquids.

Figure. Incidence of achalasia in Hong Kong



In the study, almost all patients underwent esophagogastroduodenoscopy, which commonly revealed a dilated esophagus with food residue. Barium swallow and manometry were also performed, both having similar diagnostic yields.

The majority of the patients received pneumatic balloon dilation as the initial treatment; however, only 68% showed good response. There was a small number who required several dilations before a satisfactory response was achieved. The most common complications were reflux esophagitis and perforation. Where indicated, laparoscopic myotomy was the main surgical procedure performed, with 82% of patients having a persistent satisfactory response. Botulinum toxin injection also produced a positive long-term response, especially in patients older than 50 years. Response to medications like calcium channel blockers, famotidine, and cisapride was generally poor.

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HBsAg quantification: From research tool to standard diagnostic test

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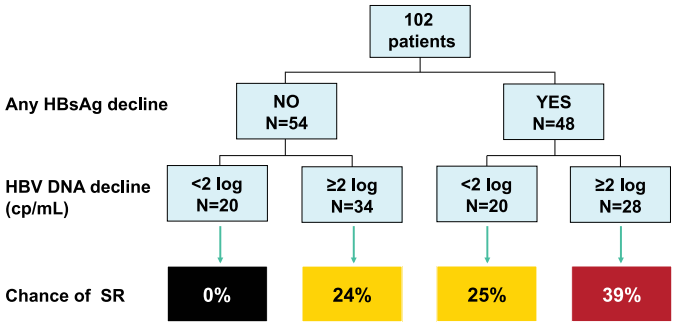
Monitoring the effectiveness of antiviral therapy is essential in predicting the outcome of hepatitis B virus (HBV) infection as well as in tailoring drug dose and schedule to the needs of the individual patient. With the rising resistance rates to antiviral agents, a diagnostic marker that can predict treatment response will prove to be a valuable and likely cost-effective clinical tool. While hepatitis B surface antigen (HBsAg) quantification appears useful and has been under investigation for several decades, genomic quantification has become the gold standard for monitoring disease progression, primarily because the former involved a labour-intensive, multi-step process. With the advent of commercial assays, however, HBsAg quantification is gaining increasing recognition.

Professor Tillman enumerated several instances when a quantitative HBV viral antigen assay is considered particularly valuable: when it is cheaper than a genomic test; when it is more sensitive than other assays; and when it can disclose additional information especially during the chronic phase of disease.[1] It is likely to be cheaper in most if not all instances, as we learned it is not a substitute to other tests but gives different or further information.

For example, quantitative HBsAg has been found to be much more useful than HBV-DNA in determining hepatitis B immunoglobulin (HBIg) requirement in the setting of liver transplantation.[2] Likewise, quantitative measurement of HBsAg rather than HBV-DNA levels is a better predictor of response to interferon therapy,[3,4] thereby permitting earlier identification of ideal treatment candidates.

The role of quantitative HBsAg outside of interferon therapy and liver transplantation remains unclear at present, but it might be useful for treatment monitoring when HBV-DNA has become undetectable, and might also be helpful in predicting prognosis. However, such studies are still to be done.

Figure. Interferon-stopping rule at week 12 based on HBsAg and HBV-DNA



HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; SR, sustained response

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PET/CT in detection of peritoneal carcinomatosis from colonic malignancy

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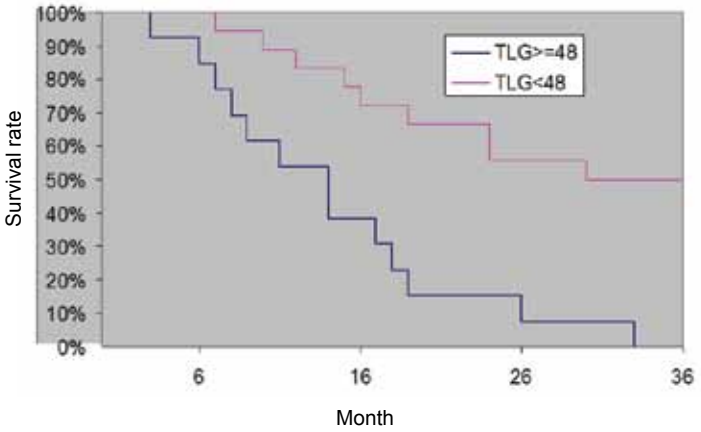
Early detection of peritoneal carcinomatosis (PC) remains a diagnostic challenge, even as new treatment approaches, particularly cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC),[1,2] are paving the way for enhanced patient survival. According to Dr Ho, limitations in the usefulness of conventional imaging techniques can be attributed to the anatomic complexity, large surface area, high free-flow mobility, and extensive lymphatic network of the peritoneum. In addition, radiographic lesion patterns and disease progression can change significantly even in individual patients, necessitating constant vigilance for subtle but key findings.[3]

Compared with computed tomography (CT) or positron emission tomography (PET) alone, the combination of PET/CT has demonstrated markedly improved accuracy in detecting PC,[4,5] but requires a thorough understanding of the mechanisms involved in the metastatic spread of peritoneal malignancies, namely, peritoneal fluid flow and lymphatic drainage.[6] Results of a recent study by Dr Ho and colleagues using PET/CT support the following conclusions:

- In colonic cancer, detection of metastases to portal, coeliac and superior mesenteric nodes (sentinel nodes) should alert the clinician to the presence of peritoneal seedings.
- Supraclavicular node involvement is probably the worst sign of peritoneal carcinomatosis and represents an "escaped" metastasis.
- The summation of total lesion glycolysis in all peritoneal cancer deposits (PCTLG) can be considered the functional analogue of the peritoneal cancer index (PCI),[7] and may be a better indicator of PC burden.

Figure. Prognostication by PCTLG



TLG, total lesion glycolysis

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Natural History of Chronic Hepatitis C: Genotype 1 versus Genotype 6 (Summary of Dissertation 2010)

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Literature Review on Chronic Hepatitis C and its Genotypic Variability

Hepatitis C virus (HCV) – virus of genetic heterogeneity

HCV is classified within the family *Flaviviridae*, where all members are small enveloped viruses containing a positive-sense single stranded RNA encoding a viral polyprotein. The HCV RNA polymerase is error prone because it lacks a proofreading exonuclease. During viral replication, random uncorrectable nucleotide errors are inevitably introduced, resulting in a heterogeneous population of viral genomes. HCV also has a high spontaneous nucleotide substitution rate with a frequency of 10^{-2} to 10^{-3} substitutions per nucleotide site per year. Any non-lethal substitution can result in amino acid changes and has the potential to alter the biology of the virus. Thus HCV is a heterogeneous virus, with many variants showing only 68-79% similarity to one another.

The marked genetic heterogeneity of HCV led to different and confusing classifications of HCV genotypes in the early 1990s. The differences in classifications were eventually resolved in 1994 by a consensus paper by Simmonds et al [1], proposing to classify HCV genotypes based on phylogenetic analysis of nucleotide sequences of complete genomes or subgenomic genomes. Plasma samples from patients infected with HCV were collected from Europe, North and South America, and the Far East. Isolates of the same genotype had an average sequence homology of 95%, with a range of 88% to 100% on the basis of sequencing 3 HCV genomes: E1, NS4 or NS5. Simmonds et al chose NS5-specific primers to amplify the extracted RNA samples, mainly because the NS5 region has up to 44% sequence divergence between different HCV genotypes.

Results from the sequenced data enable the construction of a phylogenetic tree, where major genotypes are assigned a number and subtypes within each genotype with a small letter (Figure 1). There are six HCV genotypes and over 100 subtypes. Each closely related subtype has a 20 to 25% difference in nucleotide sequencing, compared to more than 30% for different genotypes. Subsequent reports proposed additional genotypes of 7 to 11; however repeated phylogenetic analysis have shown that these isolates can be classified under either genotype 3 or 6.

Distribution of HCV genotypes by geography, age and race

HCV genotype 1 is the most common genotype worldwide, and accounts for 70% of cases in the United States, with genotype 1a and 1b having a similar prevalence. Genotype 1b is especially prevalent in Southern and Eastern Europe, China and Japan, where it accounts for the majority of infections. HCV genotype 2 also has a global distribution, but is less common than genotype 1. Genotype 3 is seen in various regions throughout the world, but is more common in South Asia and Australia. Genotype 4 is found in the Middle East and Africa, especially in Egypt. Genotype 5 accounts for 50% of genotypes seen in South Africa, and is rarely seen outside Africa. Genotype 6 is seen in Southern China and Southeast Asia (Figure 2). Unlike genotypes 1 to 3, genotypes 4 to 6 are noted for their geographic segregation. It has been suggested that all HCV genotypes diverged and evolved in isolation, beginning probably 500 to 2000 years ago. However, genotypes 1 to 3 became more widely distributed due to population migration within the last 50 to 300 years [2].

Each geographical region has a different degree of genetic diversity irrespective of genotype. Genotype 1, 2 and 4 have a remarkable diversity of subtypes in West Africa; studies there had identified 20 different subtypes of genotype 2. Genotype 3 and 6 also show similar diversity in South and Southeast Asia. This is markedly different from the relatively few subtypes of genotype 1 and 2 found in Europe or North America. The differences in regional genetic diversity suggests that HCV has been endemic in West Africa and Southeast Asia for a considerable time, while the occurrence of infection in Western countries represents a relatively recent emergence of the infection. The more recent infection in Western countries could be due to the widespread use of unsterilized needles for injections and vaccinations since World War II. Genotype 4 is widespread in Egypt probably due to the parenteral treatment of schistosomiasis using non-sterilized needles in the 1950s and 1960s [3]. Thus only one common subtype (genotype 4a) is found in Egypt, while multiple subtypes of genotype 4 had been isolated in Tanzania.

Evidence of long-standing infection in certain geographical regions led to one of the great mysteries of HCV - how did transmission occur during historical times when there was a lack of parenteral exposure? Transmission of HCV from mother to child or by sexual contact is possible but inefficient, and unlikely to be responsible for the endemicity in Africa or South Asia. One postulation is the widespread prevalence of folk medicine practices, such as circumcision, body piercing, acupuncture and sacrification practices, in various endemic regions. Transmission of HCV has been documented by such methods when infection control measures are inadequate. Thus HCV had been contained in several endemic regions for possibly thousands of years, and it is due to the practice of unsafe blood transfusions, vaccine administrations, and injection drug use in recent times that HCV infection becomes a truly global epidemic.

Clinical significance of HCV genotypes - optimizing interferon therapy

Interferon was approved by the United States Food and Drug Administration (FDA) for the treatment of HCV in 1991. This was based on earlier studies showing a biochemical response in HCV patients after 6 months of interferon-alpha, although biochemical relapses after treatment cessation were frequently encountered. The duration of therapy was increased to 12 months, but a sustained response was still only achievable in only 13-25% of patients. Ribavirin was added to the standard treatment regimen almost 10 years later. Being a synthetic nucleoside analogue, it is able to induce lethal mutations in the HCV viral genome. Twelve months of combined interferon-alpha and ribavirin were able to improve the sustained virologic response (SVR) rate to 41%.

The suboptimal response rates led to research aimed at identifying factors associated with a better treatment response. Studies in the early 1990s had shown HCV genotypes influencing response to interferon treatment. Using multivariate analysis, a study concluded HCV genotype 1b to be an independent factor of poor response to interferon therapy when compared to genotypes 2 and 3 [4]. Only 29% of genotype 1 patients achieved a long-term biochemical response compared to 52% of genotype 2 and 74% of genotype 3. Other predictors of response, of lesser importance, include younger age, lower levels of pre-treatment viremia, lower body weight and favorable liver histology.

Initially developed in the 1970s, pegylation increases the molecular weight of a drug, and has the potential to increase the circulating half-life of the drug, reducing dosage frequency and toxicity without affecting the efficacy. In the case of interferon, pegylation allows the drug to be administrated once weekly instead of three times per week, without compromising drug efficacy and with no increase in drug toxicity.

When compared to conventional interferon monotherapy, pegylated interferon monotherapy was twice as effective in achieving SVR (39% versus 19%) [5]. When pegylated interferon alpha-2b was combined with ribavirin 800mg daily for 48 weeks, SVR rates reached 54%. This same study also found genotypes 2 and 3 patients having a SVR of 80% compared to 42% for genotype 1. Pegylated interferon alpha-2a plus ribavirin 1000 to 1200mg daily for 48 weeks achieved similar results. The overall SVR rate was 56%; 46% for genotype 1 and 76% for genotype 2 or 3. A study on viral kinetics also confirmed HCV genotype 1 to have a slower decline of viremia when compared to genotype 2 or 3.

The differences in treatment response for different genotypes allow researchers to adjust treatment duration according to the genotype. Hadziyannis et al [6] noted that genotype 2 and 3 patients treated with only 24 weeks of pegylated interferon and ribavirin would respond similarly to 48 weeks of therapy (84% versus 80%, $p>0.05$). For genotype 1, 24 weeks of treatment was markedly inferior to 48 weeks. Furthermore, a rapid virologic response (RVR: undetectable HCV RNA at 4 weeks of therapy) was a strong predictor of SVR (94% for genotype 2, 85% for genotype 3). Twenty-four weeks of pegylated interferon and low-dose ribavirin has become the recommended therapy for genotype 2 and 3, with genotype 2 responding better than genotype 3 when the duration of therapy was further shortened (SVR rate 82% versus 71%, $p<0.001$).

HCV genotypes 4, 5 and 6

Compared to genotypes 1, 2 and 3, genotypes 4, 5 and 6 have not been adequately represented in large multi-center clinical trials due to their low prevalence in the United States and Europe. However, there are growing interests to study the efficacy of interferon treatment in genotype 4 in recent years. A meta-analysis of 6 randomized controlled trials found SVR rates obtained with pegylated interferon and ribavirin for 1 year in genotype 4 patients to be between 55 to 72%; patients on a larger dose of ribavirin had a higher chance of achieving SVR [64]. Generally speaking, genotype 4 patients have a SVR rate slightly superior to genotype 1 but inferior to genotypes 2 and 3. Current guidelines recommend 48 weeks of treatment, similar to genotype 1. RVR has a role in genotype 4, with the SVR rate of patients achieving RVR to be 86%. In addition, genotype 4 patients achieving HCV RNA negativity at week 12 can be considered for shortening treatment to 36 weeks, with 76% of these patients achieving SVR.

There are scanty medical literature on the treatment response of HCV genotype 5. Small studies have shown a SVR rate resembling genotypes 2 and 3. One study published in abstract form found genotype 5 patients achieving a SVR rate of 71% when given interferon-alpha or pegylated interferon plus ribavirin for 1 year. Another study found a SVR rate of 63.6% after 1 year of interferon-alpha and ribavirin, compared to 66.6% for genotypes 2 or 3 and 22.7% for genotype 1.

Evidence concerning treatment response of HCV genotype 6 is also limited to small studies from Southeast Asia and Hong Kong. When treated with 1 year of interferon-alpha and ribavirin, the SVR rate ranges from 62.5 to 82.5%. When 48 weeks of pegylated interferon and ribavirin are given, SVR rate approaches 86%, compared to 52% in genotype 1. Further studies are required to determine whether 24 weeks of treatment would be sufficient for genotype 6.

The SVR rates for different genotypes when treated with pegylated interferon and ribavirin are summarized in Figure 3. While there are no direct comparison studies for all six genotypes, it would seem the treatment response rates from best to worst are in the following order: 2, 3, 6, 5, 4, 1.

Genotypes affecting treatment outcome – is there an explanation?

Why is HCV treatment outcome genotype-specific? While recent research has led to an increased knowledge in the interaction between HCV, interferon and ribavirin, the underlying mechanism of how genotypes influence treatment outcomes is still poorly understood.

Different hypotheses have been proposed based on the fact that HCV and the host immune response are closely related. One study found genotype 1 patients to have an increased up-regulation of interferon stimulated genes (ISG) when compared to genotypes 2, 3 and 4, causing immune dysfunction and poor treatment outcome. Another study suggested genotype 1 to be the most resistant of all genotypes to interferon-induced ribonuclease (RNaseL), which is involved in the destruction of viral RNA. Another hypothesis involves the

double-stranded RNA-dependent protein kinase (PKR), which is activated by interferon. HCV proteins E2 and NS5A are capable of inhibiting PKR activation. It has been observed that the NS5A protein from genotype 1b is more capable of inhibiting PKR activation when compared to genotype 2a. The ability of E2 to inhibit PKR was also found to be specific to genotype 1.

The evolutionary diversity of HCV genotypes led to Pang et al proposing a new hypothesis: clinical response rates to interferon-based therapies are a reflection of HCV evolutionary adaptations to the immune system, and not associated directly to modern interferon therapy itself [7]. Using HCV genomic sequencing of all 6 genotypes from the European HCV database, individual phylogenetic analysis of each genotype was performed (Figure 4). It revealed that HCV genotype 2 branched out first in evolutionary history, followed by genotypes 3, 5 and 6. Genotypes 4 and 1 branched out last. Thus with a younger evolutionary genotype age, there was an increase in clinical resistance to interferon. This indicates the evolutionary pattern of HCV may result in a selective pressure favoring adaptations to the immune system resulting in greater clinical resistance. Pang et al also found the two regions of the HCV genome most associated with interferon resistance: E2 and NS5A; the exact two proteins able to inhibit PKR activation.

Recent research has also identified an additional factor probably as important as genotype in determining treatment outcome. Based on a genome-wide association study (GWAS) on HCV genotype 1 patients in a Japanese population, several single nucleotide polymorphisms (SNPs) near the gene IL28B on chromosome 19 were significantly associated with SVR. The authors concluded that testing for IL28B polymorphisms could replace current viral kinetics in determining treatment duration. Genetic polymorphisms in the IL28B region are also associated with a better treatment response in genotype 1 patients with European ancestry and African-American. IL28B polymorphisms are seen more frequently in European than African populations; this could explain the difference in response rates in the two racial groups. Further research would be needed for other genotypes and to define the role of IL28B in tailoring management for HCV patients.

Conclusion

Twenty one years ago, HCV was still undiscovered. Yet in two decades, we have seen an explosion in medical research in our understanding of HCV. Twenty one years ago, NANBH was a disease of unknown etiology resulting in a global epidemic. Now, there are genotype-specific treatment regimens and good predictive factors concerning treatment outcome. With the advancement of genomic sequencing, we now have a more in-depth understanding of HCV, and with this newly gained knowledge, hopefully treatment outcomes can be further improved in the future.

Study

Introduction

Chronic HCV infection is also known for its high degree of genetic heterogeneity, with 6 major genotypes identified. Most studies report findings of genotype 1-3, though a large number of patients worldwide have genotype 4-6. HCV genotype 6 is mostly found in South East Asia, including China, Taiwan, Macau, Vietnam, Thailand and Myanmar. The prevalence of genotype 6 among HCV carriers ranges from 18% in Thailand, 23.6% in Hong Kong, and 49% in Myanmar. It is the second most common genotype in southern China after genotype 1, and one of the most common genotypes in South East Asia, where an estimated 32.3 million are infected. HCV genotype 6 is also known to be commonly found in intravenous drug users, with a study in Hong Kong showing a prevalence of 58% among drugs users with chronic HCV.

Disease progression in chronic HCV is influenced by both host-related and viral-related factors. Concerning viral genotype, results from various studies have been conflicting. In all these studies, very few patients with HCV genotype 6 were recruited. There is thus scarcity in literature on the natural history of HCV genotype 6, and its comparison to other HCV genotypes.

Methods

The present study was performed in the University Department of Medicine, Queen Mary Hospital, Hong Kong. All medical records of patients positive for antibody to HCV (anti-HCV) from 1991 to 2007 were reviewed. Patient characteristics and demographic information, as well as the route of transmission, suspected date of contracting the infection and date of presentation were retrieved. Baseline laboratory investigations at their initial visit were recorded. Patients were observed for the occurrence of cirrhotic complications, including HCC, ascites, varices, hepatic encephalopathy (HE) and spontaneous bacterial peritonitis (SBP). They were also observed for mortality and liver transplantation. For patients who subsequently received interferon and ribavirin treatment in their follow-up, the data for the present study of natural history were censored at the date of starting treatment.

The inclusion criteria consisted of patients positive for anti-HCV and HCV RNA who had been followed up for more than 6 months. Patients concomitant chronic liver disease, or with cirrhotic complications, history of interferon therapy or liver transplantation prior to presentation or within 6 months of follow-up were excluded. For patients requiring liver transplantation during follow up, the date of transplantation was regarded statistically as mortality. Quantitative HCV RNA was determined by real-time quantitative PCR with the Applied Biosystems-7700 sequence detector system (Perkin Elmer Corp. / Applied Biosystems, Foster City, California). HCV genotypes were determined using the Linear Array Detection Kit (Roche Molecular Systems Inc.) in accordance with the manufacturer's instructions, which allows determination of HCV genotypes 1 to 6.

All statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, Illinois). The Mann-Whitney U-test was used for continuous variables with a skewed distribution; Pearson's chi-squared test was used for categorical variables. The Kaplan-Meier method using the Log Rank test was applied for the cumulative rate of cirrhotic complications and mortality for the comparison between the two genotypes. A two-sided p value of <0.05 was considered statistically significant.

Results

In total, 451 patients positive for anti-HCV were referred to our center from 1991 to 2007 (Figure 5). Of these, 101 patients were negative for HCV RNA and excluded from analysis. Of the remaining 350 patients with active infection, 220 (62.9%) had genotype 1 while 101 (28.9%) genotype 6. Applying the exclusion criteria mentioned above, 138 genotype 1 and 78 genotype 6 patients were recruited in the present study. There were no significant differences in the baseline age, sex and ALT of both the included cohort and excluded patients for the two genotypes. The baseline demographic data are summarized in Table 1.

For genotype 1 patients, 71.7% of patients acquired chronic HCV through blood transfusion, while only 8.7% were intravenous drug users. This distribution was significantly different ($p<0.001$) when compared to genotype 6 patients in whom 56.4% and 28.2% acquired the infection through blood transfusion and intravenous drug use respectively.

Baseline liver biochemistry is summarized in Table 1. There were no significant difference in the baseline ALT, albumin, bilirubin, AFP and HCV RNA between the two groups. Based on the liver function during follow-up, the median ALT levels of both genotypes were compared, and were categorized into normal, 1 to 2 times the upper limit of normal, and greater than 2 times the upper limit of normal (Table 1). Again there was no significant difference between the two groups ($p=0.121$).

Thirty-one patients (22.5%) with HCV genotype 1 and 19 patients (24.4%) with HCV genotype 6 developed cirrhotic complications. For genotype 1, 11 (35.5%) patients developed HCC, 12 (38.7%) developed esophageal varices, 6 (19.4%) developed ascites, 1 (3.2%) developed HE and 1 (3.2%) developed SBP. For genotype 6, 7 (36.8%) patients developed HCC, 11 (57.9%) developed esophageal varices and 1 (5.3%) developed ascites. The cumulative occurrence of cirrhotic complications is illustrated in Figure 6. Throughout the period of follow-up, there was no significant statistical difference in the cumulative rates of cirrhotic complications between genotype 1 and 6

patients (p=0.358). The cumulative rate of liver-related mortality is depicted in Figure 7. 8.8% of HCV genotype 1 and 7.7% of HCV genotype 6 had liver-related mortality or required liver transplantation. There was again no significant statistical difference in the mortality rate (p=0.649).

Discussion

In the present study, 28.2% of genotype 6 patients were intravenous drug users, a figure similar to previous epidemiological studies in our locality [8]. A statistically significant proportion of HCV genotype 6 patients were intravenous drug users, which supports the findings of previous studies. The epidemiology of HCV transmission has been changing in recent decades. The major mode of transmission in the developed world is intravenous drug use, while in the developing world, unsafe blood transfusions are the more common route of transmission. This change in the mode of transmission may also affect the HCV genotypic distribution over time. An epidemiological study in the United States during the 1990s found HCV genotype 1 to be more common in elderly patients [9]. Genotype 1 was found to be more common in patients acquiring the infection in the 1960s and 70s, while other genotypes are usually acquired in the 1980s or later. It has been hypothesized that HCV genotype 1 is commonly transmitted in the 1960s and 1970s by blood transfusion, while intravenous drug use in more recent times play a more important role in transmitting other genotypes. This is likely to be true also for HCV genotype 6.

Previous studies on the natural history of HCV have used various outcome measures to compare different genotypes, including the development of cirrhotic complications, HCC and mortality; none had specifically studied HCV genotype 6. To our knowledge, this is the first study comparing the natural history of HCV genotype 1 and 6. The major finding of this study is that HCV genotype 1 and 6 share a similar natural history based on liver biochemistry, HCV viral load, and on the probability of cirrhotic complications and mortality after a median follow-up period of over 5 years. The results of the present study adds to the general growing consensus that viral genotype is not a main determining factor of disease outcome. Instead, HCV viral genotype is more relevant as a predictor of response to interferon therapy.

There were limitations to our study. Firstly, as HCV genotyping was determined by linear array detection instead of the reference standard of direct sequencing, there was the potential for mistyping genotype 6 subtypes (previously known as genotype 7-9) as genotype 1. These genotype 6 subtypes, which include 6b, 6d, 6g, 6h and 6k, were found in other regions in Southeast Asia including Burma and Vietnam, but were not present in a Hong Kong study consisting of 1055 patients. Thus, it was unlikely that genotype 6 subtypes were mistyped in our present study. The route of infection and its date is based on the history given by the patients, and it would not be possible for the investigators to verify the accuracy. The age at the time of initial infection has been previously shown to be associated with the rate of disease progression, a later age of infection being associated with a more rapid disease [10]. This variable was not included in our analysis, since with the sizable proportion of patients being intravenous drug users, it would be impossible to determine the date of exact infection for these patients.

In summary, HCV genotype 1 and 6 shared similar liver biochemistry, HCV viral load, and more importantly, a similar cumulative rate of development of cirrhotic complications and mortality. Further larger studies are needed for a more comprehensive understanding of disease progression in HCV genotype 6, given its growing importance in the Asian population.

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Table 1. Baseline demographic and follow-up data of patients with genotypes 1 and 6

Patient Characteristic		Genotype 1 (n=138)	Genotype 6 (n=78)	*p* value
Age		50.0 (17-81)	46.5 (12-82)	0.342
Male		59.4%	56.4%	0.667
Route of transmission				
- Transfusion		71.7%	56.4%	<0.001
- IV drug addiction		8.7%	28.2%	
Duration of infection (years)*		19 (1-37)	20 (1-30)	0.672
Follow-up years		5.91 (0.5 – 23.3)	5.42 (0.5 – 14.7)	0.230
ALT (U/L)		65.0 (4-524)	77.5 (13-570)	0.262
Albumin (g/L)		43.0 (17-53)	43.0 (31-52)	0.648
Bilirubin (μmol/L)		12.0 (2-140)	11.5 (3-57)	0.591
AFP (ng/mL)		5.0 (1-264)	5.0 (1-151)	0.684
HCV RNA (log IU/mL)		5.24 (2.39-14.9)	4.94 (2.30-14.9)	0.232
Median ALT during follow-up	< 1 x ULN	38.4%	29.5%	0.121
	1-2 x ULN	36.2%	32.1%	
	> 2 x ULN	25.4%	38.5%	

Continuous variables expressed in median (range)

ULN = Upper limit of normal

*Duration of infection is only applicable to transfusion-related cases. 7 cases of genotype 1 and 4 cases of genotype 6 had uncertain date of transfusion.

Figure 3. The SVR rates of pegylated interferon and ribavirin for the 6 HCV genotypes [57, 59, 61, 65, 66, 70, 120] (not a direct comparison)

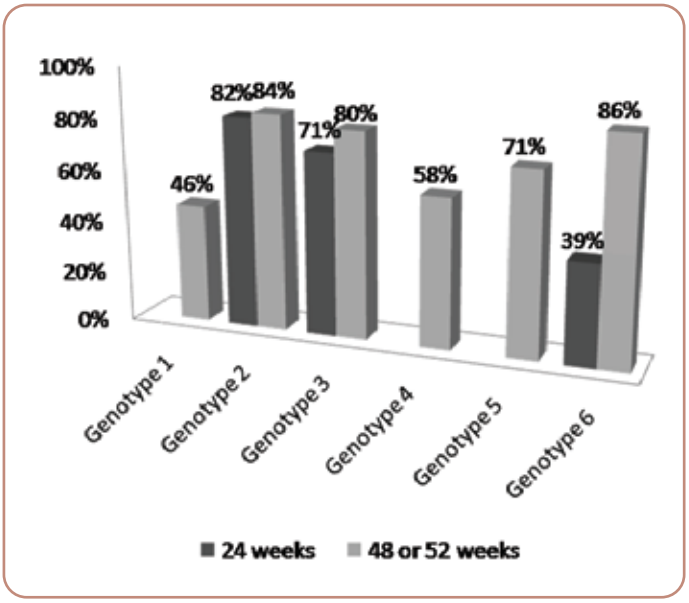
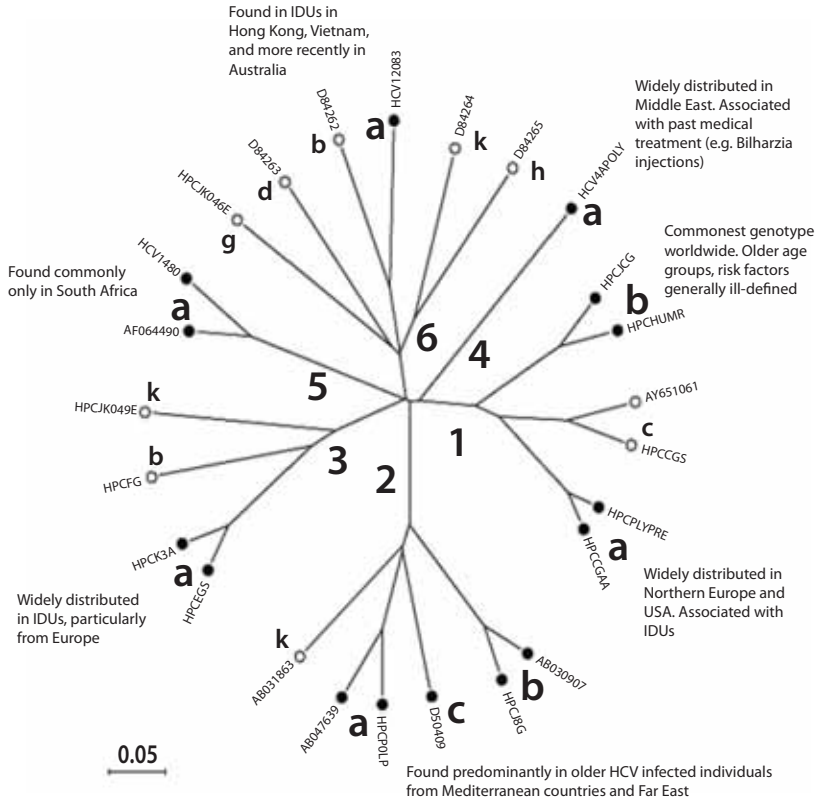
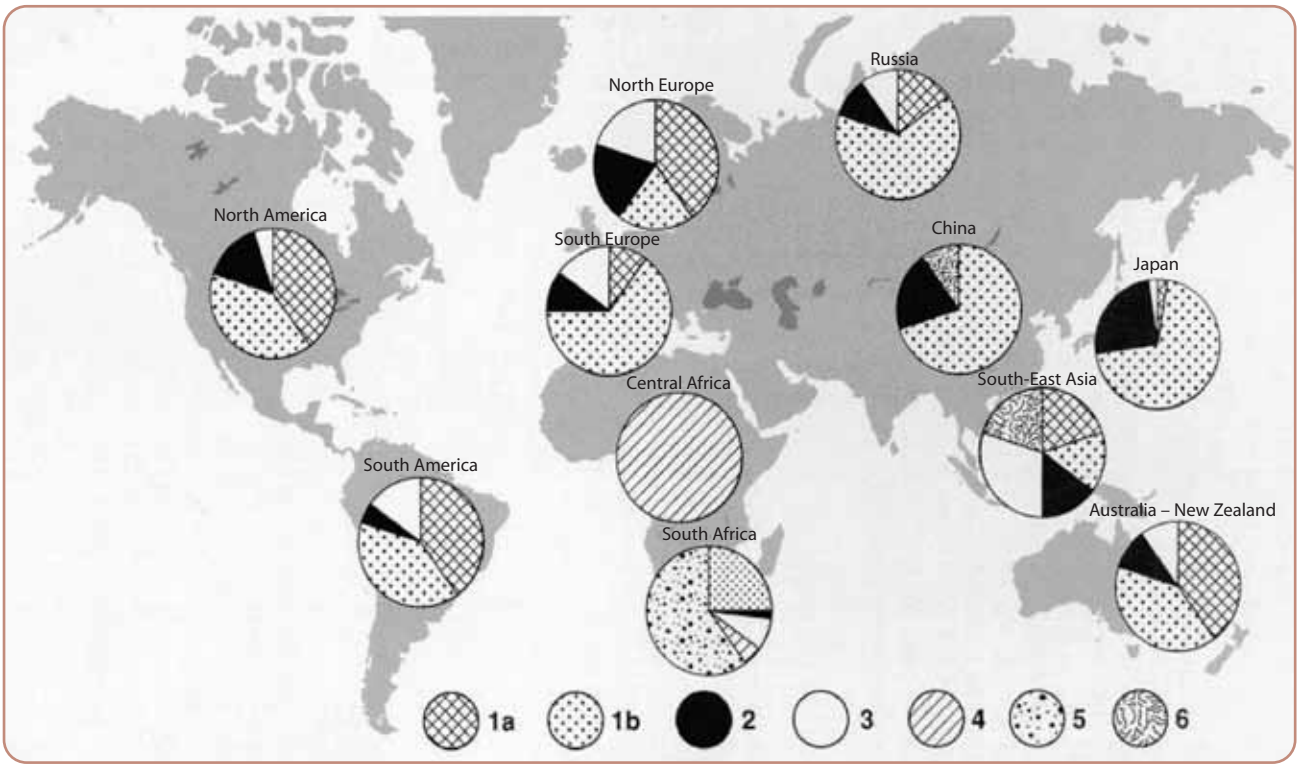


Figure 1. Phylogenetic tree of the HCV genome



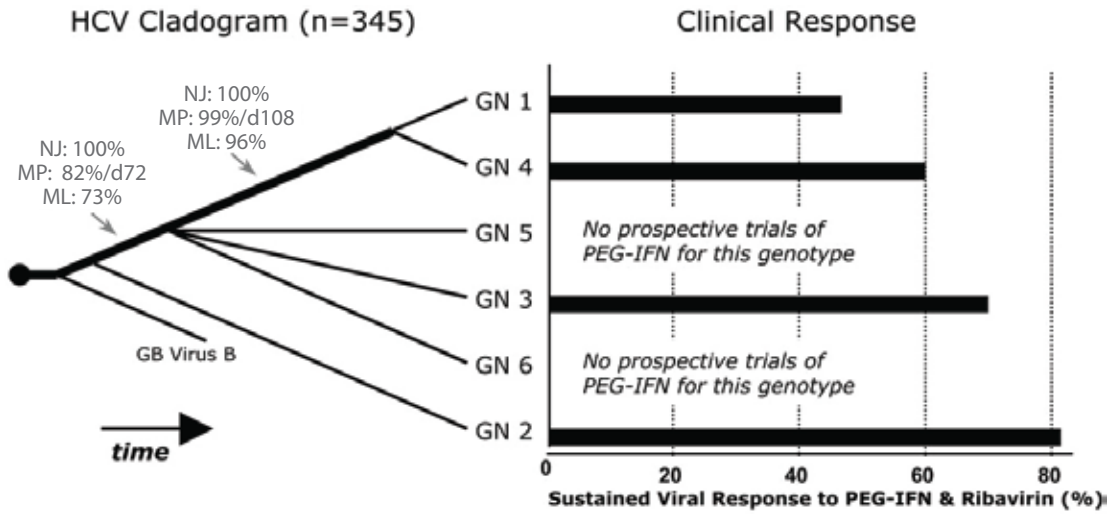
Adopted from Simmonds P, Bukh J, Combet C, et al. Consensus proposal for a unified system of nomenclature of hepatitis C virus genotypes. Hepatology 2005; 42: 962-73.

Figure 2. Geographical distribution of HCV genotypes



Adopted from Forns X, Bukh J. The molecular biology of hepatitis C virus. Genotypes and quasispecies. Clin Liver Dis 1999; 3(4): 693-716.

Figure 4. Phylogenetic analysis of 345 full-length HCV genomic sequences



Adopted from Pang PS, Planet PJ, Glenn JS. The evolution of the major hepatitis C genotypes correlates with clinical response to interferon therapy. PLoS 2009; 4(8): e6579.

Figure 5. Flow chart on cohort selection

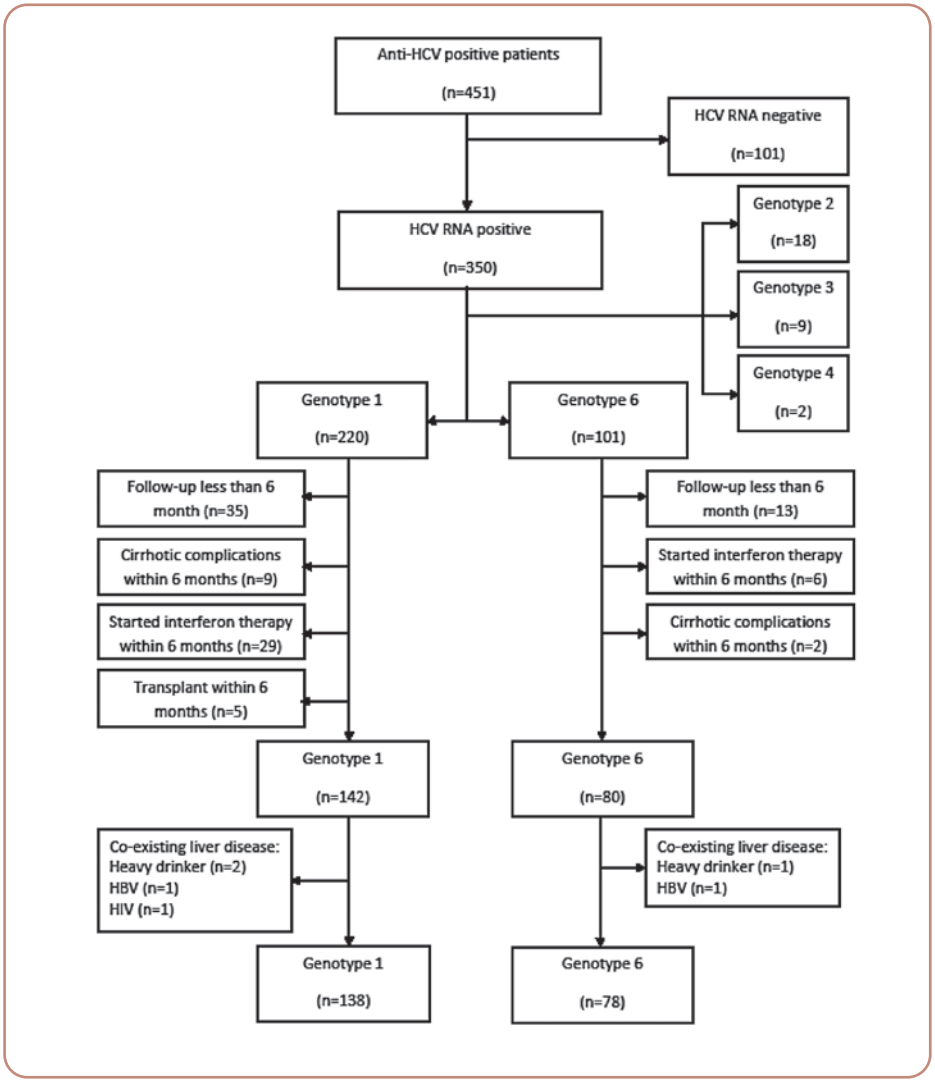
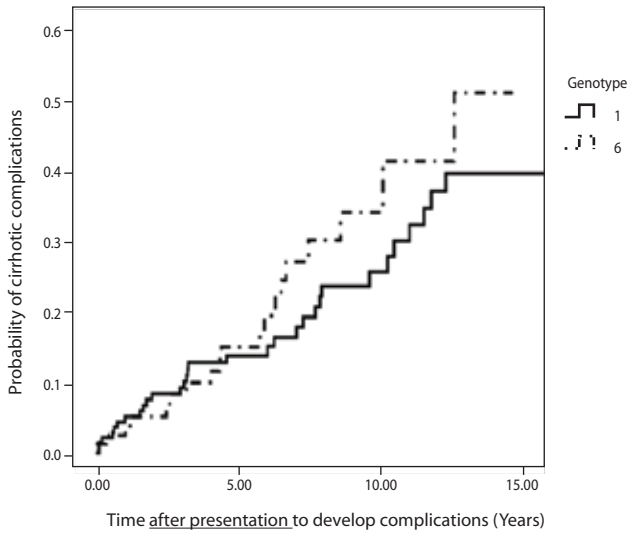
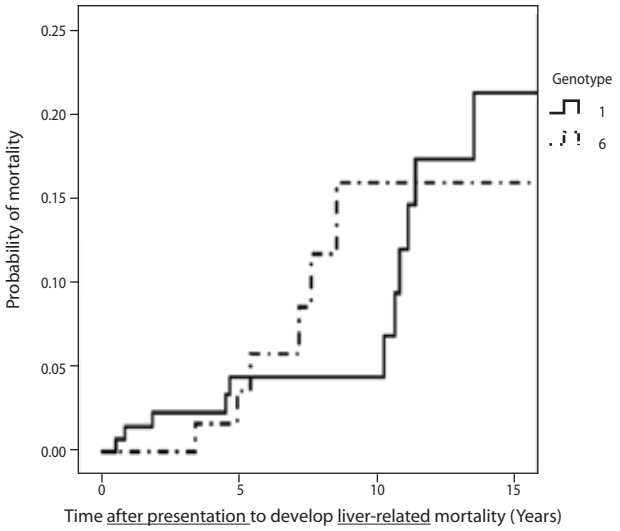


Figure 6. Kaplan-Meier actuarial analysis of time to develop cirrhotic complications for HCV genotype 1 and 6 (p=0.358)



Number of patients at risk	Genotype 1	138	121	113	106
	Genotype 6	78	68	61	59

Figure 7. Kaplan-Meier actuarial analysis of time to mortality for HCV genotype 1 and 6 (p=0.649)



Number of patients at risk	Genotype 1	138	133	133	126
	Genotype 6	78	76	72	72

13th JOINT ANNUAL SCIENTIFIC MEETING

Date : 10 September 2011 (Saturday)

Venue : Level 7, Langham Place Hotel
555 Shanghai Street, Mongkok
Kowloon, Hong Kong

Organizing Chairperson: Dr. Annie O.O. Chan

Sponsors : AstraZeneca Hong Kong Limited &
Bristol-Myers Squibb Pharma (HK) Ltd.

Co-organized by:
The Hong Kong Society of Gastroenterology
Hong Kong Society of Digestive Endoscopy
Hong Kong Society for Coloproctology
The Hong Kong Association for the Study of Liver Diseases
The Hong Kong Society of Gastrointestinal Motility
Hong Kong IBD Society

Topics	Speakers
Rifaximin therapy and IBS	Prof. Anthony Lembo (USA)
Biological therapy for IBD: When to Start, When to Stop, Which Drug to Choose, and How to Predict Response?	Prof. Geert R. D'Haens (The Netherlands)
Prevention - How to prevent post-infectious IBS? IBS and antibiotics	Prof. Anthony Lembo (USA)
Prevention of post-operative recurrence in Crohn's disease	Prof. Geert R. D'Haens (The Netherlands)
Management of chronic hepatitis B: an Update	Prof. Vincent Wong (PWH)
Serological diagnosis in GI and liver disease	Dr. Eric Y.T. Chan (QMH)
GERD update	Prof. Justin C.Y. Wu (CUHK)
Image-Enhanced Endoscopy in the Colon : Is the Future Bright?	Prof. Philip W.Y. Chiu (CUHK)
Local experience on colorectal ESD	Prof. Simon Ng (PWH)
Modern Management of Fistulising Crohn's disease	Dr. Siew C. Ng (CUHK)

Coming Soon

30th ANNIVERSARY SCIENTIFIC MEETING of The Hong Kong Society of Gastroenterology

Date : 9 December 2011 (Friday)

Venue : Ballroom, 3/F, Sheraton Hong Kong Hotel & Towers
20 Nathan Road, Kowloon, Hong Kong

(The program will be available soon from http://www.hksge.org.event.htm)

Welcome! New Honorary Fellow

Professor Jaw-Town Lin
Dean of College of Medicine
I-Shou University
Kaohsiung, Taiwan

Highlights

30th Annual General Meeting cum Scientific Meeting

10 March 2011, Langham Place Mongkok, Hong Kong

Organizing Chairman: Professor Justin C.Y. Wu

The scientific meeting was successful attended by 125 specialists and medical practitioners. Professor Jaw-Town Lin from the I-Shou University, Kaohsiung, Taiwan was the distinguished guest awarded Honorary Fellowship of the Society. In commemoration of the award, he was presented a plaque of the Society by Professor Benjamin Wong, President of the Society.

Professor Lin delivered a talk on "The causes and prevention of gastric cancer". His talk was enlightening and well received.

The subsequent digestive disease case discussion focusing on "Two patients with obstructive jaundice" was very informative and aroused a number of questions from the floor.

The Annual General Meeting was attended by 54 fellows and members during which the Society's annual report and financial statements for the year of 2010 were presented by the Chairman and Hon. Treasurer respectively. Six Council members were re-elected to the Council for the term 2011-2013.

A Certificate of Appreciation was presented to each of the thirteen sponsors in appreciation of their support and contributions towards the meeting and they were Abbott, AstraZeneca, Bristol-Myers Squibb, Eisai, Ferring, Reckitt Benckiser, GlaxoSmithKline, IDS, Novartis, Nycomed, Pfizer, Roche and Takeda.

Most participants stayed for dinner and continued exchanging their views.

Major Meetings

11-12 June 2011
The International Digestive Disease (IDD) Forum 2011: "Pioneering Research and Practice"
Organized by: Institute of Digestive Disease, The Chinese University of Hong Kong
Location: HKCEC, Hong Kong
Website: www.iddforum.com

20-23 June 2011
ACPGBI Annual Meeting
Organizer: Association of Coloproctology of Great Britain & Ireland
Location: Birmingham, United Kingdom
Website: www.acpgbi.org.uk/events/acp_conf

22-25 June 2011
13th World Congress on Gastrointestinal Cancer
Organizer: European Society for Medical Oncology
Location: Barcelona, Spain
Website: www.worldgicancer.com

3-7 July 2011
2011 Tripartite Colorectal Meeting
Organizer: The Association of Coloproctology of Great Britain and Ireland
Location: Cairns, Australia
Website: www.tripartite2011.org/

16 July 2011
Hong Kong Surgical Forum - Summer 2011
Organisers: Department of Surgery, The University of Hong Kong
Queen Mary Hospital & Hong Kong Chapter of American College of Surgeons
Location: Queen Mary Hospital, Hong Kong
Website: www3.hku.hk/surgery/forum.php

30 July 2011
1st Australasian Course on Capsule and Double Balloon Endoscopy
Organizer: Given Imaging Pty Ltd.
Location: Sydney, Australia
Website: www.e-kiddna.com.au/given

11–13 August 2011
10th Asia Pacific Congress of Endoscopic Surgery
Organized by: Endoscopic and Laparoscopic Surgeons of Asia (ELSA)
Location: Singapore
Website: www.elsa2011singapore.com/site/

28 August -1 September 2011
International Surgical Week 2011 (ISW 2011)
Hosted by: International Society of Surgery (ISS) & Societe Internationale de Chururgie (SIC)
Location: Yokohoma, Japan
Website: www.isw2011.org

2-3 September 2011
Falk Symposium 178
Diverticular Disease: A Fresh Approach to a Neglected Disease
Organizer: Falk Foundation
Location: Koln, Germany
www.drfalkpharma.de/events/international-falk-symposia-and-workshops/2011

2-4 September 2011
International Liver Cancer Association Fifth Annual Conference (ILCA 2011)
Organizer: International Liver Cancer Association
Location: Hong Kong, China
Website: www.ilca2011.org/

8-12 September 2011
18th International Meeting on Hepatitis C Virus and Related Viruses
Location: Seattle, WA, USA
Website: www.hcv2011.org/

10 September 2011 (Saturday)
13th Joint Annual Scientific Meeting
Organized by:
The Hong Kong Society of Gastroenterology
Hong Kong Society of Digestive Endoscopy
Hong Kong Society for Coloproctology
The Hong Kong Association for the Study of Liver Diseases
The Hong Kong Society of Gastrointestinal Motility
Hong Kong IBD Society
Location: Langham Place Hotel, Mongkok, Kowloon, Hong Kong
Program: (Please visit http://www.hksge.org/event.htm)

12-13 September 2011
XXIVth International Workshop on Helicobacter and related bacteria in chronic digestive inflammation and gastric cancer
Organizer: European Helicobacter Study Group
Location: Dublin, Ireland
Website: www.helicobacter.org

12-14 September 2011
International Congress of Endoscopy (ICE 2011)
Hosted by: World Organization of Digestive Endoscopy
Location: Los Angeles, USA
Website: www.ice2011.org/

12-15 September 2011
Australian Gastroenterology Week (AGW2011)
Organizer: Gastroenterological Society of Australia
Location: Brisbane, Queensland, Australia
Website: www.agw2011.com

21-24 September 2011
ESCP 6th Scientific & Annual Meeting
Organizer: European Society of Coloproctology (ESCP)
Location: Copenhagen, Denmark
Website: www.escp.eu.com/copenhagen-2011

27-30 September 2011
The 3rd Biennial Asian Pacific HPBA Congress Melbourne 2011: Making a difference with new technologies
Location: Melbourne, Australia
Website: http://aphpba11.com/

30 September – 1 October 2011
Falk Symposium 179
Revisiting IBD Management: Dogmas to be Challenged
Organizer: Falk Foundation
Location: Brussels, Belgium
www.drfalkpharma.de/events/international-falk-symposia-and-workshops/2011

1-2 October 2011
The 2nd JSGE International Topic Conference
Organizer: The Japanese Society of Gastroenterology
Location: Japan
Website: www.apage.org/2009/events.html

1-4 October 2011
Asian Pacific Digestive Week (APDW 2011): "Integrating Science and Technology in Clinical Gastroenterology"
Organizer: Gastroenterological Society of Singapore
Location: Singapore
Website: www.apdw2011.org.sg/

9-12 October 2011
2011 International Meeting on Molecular Biology of Hepatitis B Viruses
Organizers: Michael D. Robek, Yale University School of Medicine and Maura Dandri, PhD, University Medical Center Hamburg-Eppendorf
Location: Lake Buena Vista, Florida USA
Website: www.hepb.org/hbvmeeting/

14-15 October 2011
The 5th Meeting of the Society of Gastrointestinal Intervention (SGI 2011)
Hosted by: The Society of Gastrointestinal Intervention
Location: Seoul, Korea
Website: www.sgiw.org/

20-23 October 2011
Japanese Digestive Disease Week (JDDW)
Location: Fukuoka, Japan
Website: www.jddw.jp/jddw2011/en

22-26 October 2011
19th UEGW Stockholm 2011
Organizer: United European Gastroenterology Federation
Location: Stockholm, Sweden
Website: www.uegw11.uegf.org/

23-27 October 2011
97th Annual Clinical Congress of the American College of Surgeons
Organised by: American College of Surgeons
Location: San Francisco, CA, USA
Website: www.facs.org/clincon2011/index.html

28 October – 2 November 2011
ACG 2011 Annual Scientific Meeting & Postgraduate Course
Organizer: American College of Gastroenterology
Location: Washington, DC, U.S.A.
Website: www.acg.gi.org/acgmeetings/

4-8 November 2011
The Liver Meeting 2011 & AASLD's 62nd Annual Meeting
Organizer: The American Association for the Study of Liver Diseases
Location: San Francisco, CA, USA
Website: www.aasld.org/thelivermeeting/Pages/default.aspx

9-12 November 2011
21st World Congress of the International Association of Surgeons, Gastroenterologists and Oncologists
Organizer: International Association of Surgeons, Gastroenterologists and Oncologists
Location: Tokyo, Japan
Website: www.iasgo2011.org

11-12 November 2011
Falk Symposium 180
IBD 2011: Progress and Future for Lifelong Management
Organizer: Falk Foundation
Location: Tokyo, Japan
www.drfalkpharma.de/events/international-falk-symposia-and-workshops/2011

23-25 November 2011
Annual Scientific Meeting 2011 of The New Zealand Society of Gastroenterology & NZNO Gastroenterology Nurses Section
Location: Dunedin, New Zealand
Website: www.nzsg.org.nz/meetings/new-zealand/

29 November - 2 December 2011
Ninth Annual International Congress Frontiers in Intestinal and Colorectal Disease
Organized by: St Mark's Hospital Academic Institute
Location: London, United Kingdom
Website: www.stmarkshospital.org.uk/frontiers

9 December 2011 (Friday)
30th Anniversary Scientific Meeting
Organizer: The Hong Kong Society of Gastroenterology
Location: Sheraton Hong Kong Hotel & Towers, Kowloon, Hong Kong
Program: available soon from http://www.hksge.org.event.htm