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Update in Gastroenterology

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Editor

Developments in gastroenterology continue to be in the limelight in the new millennium. Advances in basic science, laboratory technique, endoscopic procedures and imaging modalities have fuelled innovations in the diagnosis and treatment of digestive diseases. In this issue of the Diary, several disease entities have been selected for review, either because of the interest in them among practitioners or the amount of knowledge accrued in recent years. A short description of each chosen topic is given below.

It is said that the only good Helicobacter pylori is a dead one. Every effort has been made to eradicate this bug in the setting of duodenal or gastric ulcer. Eradication of H. pylori can potentially reduce the risk of gastric cancer development, particularly before the appearance of pre-neoplastic changes like atrophy and intestinal metaplasia. While a one-week course of triple therapy has been the standard treatment locally, a longer course of 14 days is used in the US. Furthermore, a novel 10-day sequential therapy has shown to be effective in a number of studies. For rescue therapy, quadruple therapy and levofloxacin-amoxicillin-based triple therapy are useful options. After successful eradication, the average annual reinfection rate is low, probably around 1%.

Gastro-oesophageal reflux-induced disease (GERD) has become the most common gastrointestinal disorder in the West and its incidence is also rising in the Asia-Pacific region. Empiric therapeutic trial of proton pump inhibitors (PPI) has been the recommended initial treatment. Endoscopy is usually performed in patients refractory to treatment, having alarm signs or symptoms or in middle age. A number of GERD patients with persistent symptoms may be benefited by PPI b.d. Extra-oesophageal manifestations have been linked to GERD, including atypical chest pain, asthma/chronic cough, laryngeal symptoms and signs, and sleep disturbance. Barrett’s oesophagus and oesophageal adenocarcinoma, as complications of GERD, are not common in Hong Kong. There are new advances in the pH and impedance studies of GERD, which increase the diagnostic accuracy. Endoscopic and surgical treatments are available for patients who refuse to take long-term medication.

Many clinicians have witnessed that the once uncommon inflammatory bowel diseases (Crohn’s Disease (CD) and Ulcerative Colitis (UC)) are now increasingly encountered in local practice. The cause of this rise is not certain but may be associated with environmental changes due to urbanisation and adoption of the western style of living, culture and diet. Higher socioeconomic class may also be implicated in disease development. The CARD15/NOD2 single nucleotide polymorphisms (SNPs) are associated with CD in Caucasians but CARD15/NOD2 mutations in Chinese CD are virtually absent. Ulcerative proctitis has been reported to be the commonest type of disease in UC, while extensive colitis is a frequent finding too.

In developed countries, nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease. NAFLD is now the most common gastrointestinal disorder in the West and its incidence is also rising in the Asia-Pacific region. Empiric therapeutic trial of proton pump inhibitors (PPI) has been the recommended initial treatment. Endoscopy is usually performed in patients refractory to treatment, having alarm signs or symptoms or in middle age. A number of GERD patients with persistent symptoms may be benefited by PPI b.d. Extra-oesophageal manifestations have been linked to GERD, including atypical chest pain, asthma/chronic cough, laryngeal symptoms and signs, and sleep disturbance. Barrett’s oesophagus and oesophageal adenocarcinoma, as complications of GERD, are not common in Hong Kong. There are new advances in the pH and impedance studies of GERD, which increase the diagnostic accuracy. Endoscopic and surgical treatments are available for patients who refuse to take long-term medication.

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In developed countries, nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease. NAFLD is now reaching an epidemic scale in Asia. In a study in China, around 15% of the adults were found to have NAFLD. The disease is certainly not
benign and can progress to liver cirrhosis, liver failure and hepatocellular carcinoma. NAFLD is closely associated with the metabolic syndrome and cardiovascular disease, and these conditions must be evaluated together. Liver biopsy has been the gold standard for disease assessment. Because of the limitations and risks of liver biopsy, non-invasive tests for liver fibrosis have been developed and they include serum biomarkers and elastography techniques (Fibroscan). Treatments of NAFLD include lifestyle management, dietary intervention, insulin sensitisers (metformin and thiazolidinediones), anti-oxidants and bariatric surgery.

An important function of the liver is the detoxification of exogenous compounds. The organ itself is, at the same time, exposed to the toxicity of these substances. Drug-induced liver injury (DILI) accounts for more than half of the cases of acute liver failure. The real incidence of DILI is not known because of the difficulty in making the diagnosis and the low frequency of reporting. The common hepatotoxic agents in clinical practice are paracetamol, amoxicillin/clavulanic acid, anti-tuberculosis drugs, thiazolidinediones, statins, etc. Another group of medications widely used in Hong Kong, which may cause liver injury, are herbal products. Antiplatelet agents are two-edged swords. On the one hand, they effectively reduce the vascular complications of atherothrombotic diseases. On the other hand, they frequently cause adverse gastrointestinal events, ranging from mild dyspepsia to life-threatening bleeding or perforation from peptic ulcer. Aspirin and clopidogrel are the two commonly used antiplatelet agents. The clinical efficacy of clopidogrel in the secondary prevention of vascular complications is marginally better than aspirin. In contrast, the incidence of severe adverse upper gastrointestinal (GI) events is significantly lower for clopidogrel compared with aspirin. Clopidogrel appears to be safer than aspirin in patients with no history of peptic ulcer disease or GI bleeding. In patients with dyspeptic or moderately severe bleeding peptic ulcers, conversion to clopidogrel or continuation of aspirin is safe if the patients are simultaneously maintained on proton pump inhibitors.

I hope this brief introduction can arouse readers’ interest in the following review articles by the experts in different areas, whose help I have the honour to enlist.

The Editor’s Message

On behalf of the Editorial Board of the Hong Kong Medical Diary, I would like to inform our readers that the editor-in-chief, Dr. Walter King, has recently decided to resign from the post and I will take up his work from now on. The Editorial Board wishes to express the gratitude to Dr. Walter King for his enormous contribution in the past few years during which he has transformed the diary into a widely circulated local medical publication and a forum for the dissemination of medical information and knowledge in various medical and dental specialties in Hong Kong. To keep up with his good work, I have to call upon all editors in the Editorial Board, all issue editors and all member societies to continue contributing comprehensive evidence-based articles of the highest quality. With the wide circulation to the 9,000 medical doctors and dentists in its distribution list and the internet version on the web page of the Federation of Medical Societies of Hong Kong, I certainly hope that both our medical and dental colleagues as well as the general public can easily find the relevant medical information and services in Hong Kong when needed.

Dr. Mok Chun On
Editor-in-chief
Hong Kong Medical Diary

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Only Quality & Fidelity is Worthy of a Lifetime Trust
Helicobacter pylori - The Legendary Bug

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Helicobacter pylori is a helical shaped, microaerophilic, flagellated Gram-negative bacterium. Its discovery dated back to 1875 but it could not be grown in culture at that time. In 1979, the bacterium was rediscovered by Dr. Robin Warren. Dr. Barry Marshall joined the research in 1981. They published the association of the bacteria and gastritis in 1983. In recognition of their discovery, Drs. Warren and Marshall became Nobel Laureates in 2005.

Epidemiology

Nearly half of the world population is infected with H. pylori. Its prevalence correlates inversely with the socio-economic status of a country. Using a commercial enzyme-linked immunosorbent assay kit for anti-HP IgG antibody on 397 volunteers who attended medical health exhibitions in October 1993 and May 1994, prevalence of H. pylori infection was found to be 58.4% in Hong Kong. More than 90% of duodenal ulcer patients were infected. H. pylori positive patients develop duodenal ulcer at a rate of ~ 1% per annum. A lower prevalence of H. pylori is observed in patients with gastric ulcer, a higher proportion of which is related to the use of aspirin and non-steroidal anti-inflammatory drugs.

The bacteria have been isolated from faeces, saliva and dental plagues of infected patients. The routes of transmission are suggested to be gastro-oral and faecal-oral. An epidemiological study performed in Melbourne Chinese immigrants showed the use of chopsticks as a risk factor for H. pylori infection, irrespective of their socio-economic status. Leung et al. tested the hypothesis of transmission via the use of chopsticks by attempting to culture the bacteria from saliva and chopsticks of 45 infected volunteers. All cultures were negative. H. pylori was detected by PCR in the saliva from 15 (33%) infected subjects and on the chopsticks from one (2%). Twelve sets of pooled chopsticks, ten in each set, were collected from the cafeteria. Washings were obtained for PCR. H. pylori was tested positive in only two sets. This demonstrated a low risk of contracting the infection through the use of chopsticks.

Diagnosis

Various diagnostic tests are available in the market. Basically they can be divided into invasive and non-invasive tests. Invasive tests include biopsy-based rapid urease test, histology, culture and molecular tests. Non-invasive tests can further be classified into passive and active tests. Passive tests include serological testing of IgG in serum, IgA in saliva, and IgG in urine. There is a trend towards development of the office-based serology tests for rapid diagnosis. A Canadian study performed for dyspeptic patients in the primary care setting, however, found a high false positive rate of 33%. It is still early to recommend the use of near-patient tests for making a diagnosis of H. pylori infection. Active tests serve to detect the presence of H. pylori and hence they provide evidence of a current infection. Currently available active tests include the urea breath test and stool antigen test.

Before a test can be employed in the community, local validation of its accuracy is required. Tests can be done by a technician but their interpretations require medical knowledge. The accuracy of biopsy-based rapid urease test is decreased in the setting of acute ulcer bleeding due to the buffering effect of serum albumin. Albumin, by releasing hydrogen ions, buffers the alkaline effect of ammonia and suppresses the colour change of the pH indicator. It was found that H. pylori was detected in 93% of nonbleeding duodenal ulcers as compared with 71% of bleeding duodenal ulcers by the biopsy urease test. There were cases where the bacteria, failed to be detected by biopsy urease test, were identified by histology.

Achlorhydria causes false-negative urease test results (biopsy and breath tests). Without the neutralising effect of acid, H. pylori is killed by the action of its own urease. Proton pump inhibitor (PPI), antibiotics and bismuth-containing compounds can reduce the density and/or urease activity of H. pylori. When given a standard dose of PPI for treating gastro-oesophageal reflux disease, 33% of the H. pylori-infected patients were tested negative by the urea breath test. Their tests returned positive 14 days after stopping the drug. Serial changes of urea breath test results in hospitalised patients taking antibiotics for chest or urinary tract infection were studied. One third of H. pylori-infected individuals had transient false-negative results. It occurred within 24 hours of antibiotics treatment and reverted back to normal at six-week post treatment.

It has been recommended to withhold bismuth and antibiotics for at least 28 days and PPI for 14 days prior to H. pylori testing by the urea breath test. It is controversial whether H2-receptor antagonists affect test sensitivity but most laboratories would suggest to...
withhold it for 48 hours before testing.\textsuperscript{17} Despite the high sensitivity of histology, the site, numbers and size of the biopsies can have great impact on diagnostic accuracy. A single biopsy taken in the lesser curvature, close to the incisura, can detect the presence of \textit{H. pylori} in 90\% of the cases.\textsuperscript{12} Accuracy can be improved by taking additional biopsies from the greater curvature of the antrum and the greater curvature of the corpus. The American College of Gastroenterology has recommended a minimum of three biopsies to be taken for diagnosis.\textsuperscript{17}

\section*{Treatment}

The backbone of eradication therapy remains unchanged in all these years. Standard first line treatment comprises of a PPI and two antibiotics. A one-week course of this triple therapy was endorsed by The Asia-Pacific Consensus Conference\textsuperscript{20} in 1997 and The Maastricht III Consensus Report\textsuperscript{21} in 2007. In the United States, the same therapy is recommended to be given for 10 to 14 days.\textsuperscript{17} The efficacy of triple therapy has been decreasing to about 80\%.\textsuperscript{22} The drop in effectiveness is related to a rising trend of antibiotic resistance. Choice of antibiotics should be determined by the level of resistance in the locality. The European Helicobacter Study Group recommended that clarithromycin should not be used if the resistance rate reaches 15-20\%.\textsuperscript{21} In vitro metronidazole resistance is less of a concern since it does not reflect in vivo resistance. The prevalences of resistance to clarithromycin, amoxicillin and metronidazole in Hong Kong were 7.8, 0 and 39.2\% in a recent report.\textsuperscript{23} Bismuth-containing quadruple therapy has been suggested as an option for first line treatment in view of the increased resistance to both clarithromycin and metronidazole.\textsuperscript{21} Besides antimicrobial resistance, patients’ compliance plays a role in determining the success of treatment. Eradication rate dropped from 96\% to 69\% in patients who took less than 60\% of their prescribed medication.\textsuperscript{24} Although it is common to experience taste disturbance with clarithromycin and metronidazole and diarrhoea with amoxicillin, they are usually mild. Patients should be assured on the short-term nature of the side effects and encouraged to complete the course.

\section*{Sequential Therapy}

A novel 10-day sequential therapy was shown to be effective in a number of studies carried out in Italy.\textsuperscript{25-28} It consists of 5-day dual therapy with a PPI plus amoxicillin, followed by 5-day triple therapy with a PPI, clarithromycin and tinidazole. Amoxicillin has dual actions. First it helps to lower the bacterial load so as to improve the efficacy of the immediately subsequent short course of triple therapy.\textsuperscript{29} Secondly, it is speculated that, after weakening the cell wall of the bacterium, amoxicillin prevents the development of efflux channels through which clarithromycin is transferred out of the bacterium.\textsuperscript{28} In a pooled-data analysis\textsuperscript{29} of two pilot studies and 13 randomised trials on over 1800 patients, sequential therapy achieved \textit{H. pylori} eradication rate of 93.5\% at intention to treat analysis. It was found to be promising in treating antibiotics resistant organisms. Infection was cured in 16/48 patients (33.3\%) infected with clarithromycin (with or without metronidazole) resistant strains, and 68/72 patients (95.8\%) infected with metronidazole resistant strains. Compliance and side-effect profile were comparable to standard triple therapy. No difference in eradication rate was observed among different PPIs, and between patients suffering from peptic ulcer or non-ulcer dyspepsia. This new regimen, however, is not suitable for patients with penicillin allergy and its effectiveness has to be verified by centres in other parts of the world.\textsuperscript{22}

\section*{Rescue Therapy}

The principle for choosing a rescue therapy is to avoid using antibiotics which have been used in first line treatment.\textsuperscript{17} Quadruple therapy, if not given as the first line treatment, is a preferred option.\textsuperscript{21} Recently levofloxacin-amoxicillin-based triple therapy was found to be superior to quadruple therapy in two meta-analyses.\textsuperscript{30, 31} It was found to be better tolerated with a lower incidence of side effects prompting discontinuation of therapy.\textsuperscript{31} Ten-day regimens, giving an eradication rate of over 80\%, were more effective than 7-day combinations.\textsuperscript{30, 31} while no difference was observed with 500mg daily versus 250mg bd dosing of levofloxacin.\textsuperscript{31} Emergence of levofloxacin resistance strains, however, may limit its application. It is still unknown whether the resistance is absolute, as in the case of clarithromycin, or more relative as with metronidazole.\textsuperscript{17} The ten-day therapy was found to be effective in a pilot study on 35 patients who had failed the sequential regimen. The eradication rate was 85.7\% at intention-to-treat analysis.\textsuperscript{32} Rifabutin-based triple therapies were tested by several groups and found to be useful as salvage therapy.\textsuperscript{33-36} The presence of clarithromycin or metronidazole resistance did not affect efficacy of treatment.\textsuperscript{36} It is, however, limited by the potential adverse reactions characterised by fever and myelotoxicity. Large-scale use of this drug is not advisable for the fear of selecting resistance among Mycobacteria.\textsuperscript{21}

\section*{Gastric cancer}

The incidence of gastric cancer in Hong Kong is 15.6 per 100,000.\textsuperscript{37} Over 1000 new cases were diagnosed in 2005. The average mortality rate was 9.3 per 100,000. \textit{H. pylori} was classified as a grade 1 carcinogen by the International Agency for Research on Cancer in 1994.\textsuperscript{38} The infection is associated with approximately two-fold increased risk of developing gastric cancer,\textsuperscript{39} equally strong for both the intestinal and the diffuse type.\textsuperscript{40} This association is only observed for cancers developed in the non-cardiac region.\textsuperscript{41} CagA positivity further increased the risk of cancer by 2.01 fold. Searching for CagA status over \textit{H. pylori} infection may confer additional benefits in identifying populations at greater risk for gastric cancer.\textsuperscript{42} But this association may not be true in the Asian population.\textsuperscript{42} In a prospective follow-up of more than 1500 Japanese patients suffering either from upper GI pathology (peptic ulcers or gastric hyperplasia) or nonulcer dyspepsia, gastric cancers developed in 2.9\% of the infected patients after a mean of 7.8 years, but not in the uninfected individuals.\textsuperscript{43} Histology findings of corpus-predominant gastritis, severe gastric atrophy, and intestinal metaplasia put patients at an increased risk. These histological findings
were proposed as precancerous cascade in the development of gastric cancer. Apart from the infection, host genetic and environmental factors also contribute to the risk.

It remains unknown whether H. pylori eradication would reduce the risk of gastric cancer. It is unlikely that by simply removing the organism will translate into a perceptible reduction in gastric cancer risk within a short time frame. There are a number of human intervention studies looking into the effect of H. pylori eradication in the progression of precancerous lesions. It leads to the concept of ‘point of no return’.

The Chinese University of Hong Kong and the Beijing Medical University conducted a collaborative study in the county of Yantai, Shandong Province, China, where there is a high incidence (50 per 100,000) of gastric cancer. Endoscopic surveys were conducted. 587 H. pylori infected volunteers were randomised to triple therapy or placebo. Both acute and chronic gastritis and marked resolution of intestinal metaplasia decreased in both the gastric antrum and corpus and activity of intestinal metaplasia also decreased in the antrum one year after H. pylori eradication. There was, however, no regression of intestinal metaplasia or gastric atrophy. Within 5 years after H. pylori eradication, remarkable reduction in severity and activity of chronic gastritis and marked resolution of intestinal metaplasia in the antrum were observed. Continuous H. pylori infection leads to progressive aggravation of atrophy and intestinal metaplasia. In their separate report, duodenal ulcer was found to be an independent protective factor, while persistent H. pylori infection, alcohol use and drinking water from a well were independent risk factors associated with intestinal metaplasia progression. They concluded that eradication of H. pylori is protective against progression of premalignant gastric lesions. A randomised, controlled chemoprevention trial conducted in Columbia showed that by curing H. pylori infection, a modest regression of intestinal metaplasia compared with placebo (15% vs 6%) was observed 72 months. In their multivariate analysis at 12 years of follow-up on 795 patients, the preneoplastic lesions were found to regress at a rate equal to the square of time patients having free from the infection.

A randomised controlled trial was conducted in Changle County, Fujian Province, Southern China, to determine whether treatment of H. pylori infection reduced the incidence of gastric cancer. 1630 healthy H. pylori carriers were randomised for two-week triple therapy or placebo. They were followed up for an average of 7.5 years. 18 new cases of gastric cancers were reported. In the subgroup of infected volunteers without precancerous lesions (gastric atrophy, intestinal metaplasia and dysplasia) at presentation, six patients in the placebo group whereas none in the treated group developed gastric cancer. In the remaining twelve patients in which precancerous lesions were present at presentation, seven were from the treatment and five were from the placebo group. It puts forward the concept of ‘point of no return’ at which H. pylori should be eradicated before reaching the state of intestinal metaplasia in the cascade of cancer development. Eradication of H. pylori has the potential to reduce the risk of gastric cancer development, optimally before the development of pre-neoplastic lesions like atrophy and intestinal metaplasia.

### References


### Reinfecion

After successful H. pylori eradication, how often would we get re-infected? Re-infection should be distinguished from recrudescence which usually occurs early after treatment. It means reappearance of the original strain of H. pylori following its temporary suppression. One would expect high re-infection rates in countries with high prevalences of H. pylori infection. Re-infection rate was determined in 184 Chinese patients with duodenal ulcer disease who had been shown to have their H. pylori eradicated. It was conducted in Guangzhou, with a high age-standardised prevalence of ~56%. Over a period of 24 months, four patients were tested positive for H. pylori (three within six months and one at 24 months). DNA fingerprinting of isolates in one patient diagnosed H. pylori positivity at 6 month was found to have a strain identical to the pretreatment one. The average annual reinfecion rate was found to be 1.08%. Similarly low rates of re-infection were found in other Asian countries. If identical strains were considered as recrudescence, the reinfeciation rate was found to be <0.8% per patient year in a Japanese study over a period of two years.
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Medical & Dental Directory of Hong Kong, 8th Edition

On behalf of the Editorial Board, it is our great pleasure to announce the launch of the Medical & Dental Directory of Hong Kong 2007, 8th Edition.

The Federation Secretariat will notify those who have submitted their data regarding arrangement of delivery. We apologise for the delay in the production of the Directory, as it took an unexpectedly longer time to do the proof reading for the larger volume in this edition.

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Presentation: Esomeprazole film-coated tablet. Indications & Dosage: Treatment of erosive reflux oesophagitis 40mg once daily for 4 weeks. Long-term management of patients with healed erosive oesophagitis to prevent relapse 20mg once daily. Symptomatic treatment of GERD 20mg once daily, in combination with an appropriate antibacterial therapeutic regimen for the eradication of Helicobacter pylori: Healing of H. pylori associated duodenal ulcer OR as prevention of relapse of peptic ulcers in patients with H. pylori associated ulcers: 20mg esomeprazole with 1g amoxicillin & 300mg clarithromycin, all bd for 7 days. Patient requires continued NSAID therapy/healing of gastric ulcers associated with NSAID therapy: 20mg once daily for 4-8 weeks. Prevention of gastric & duodenal ulcers associated with NSAID therapy in patients at risk 20mg once daily. Contraindications: Hypersensitivity to esomeprazole; substituted benzimidazoles; hereditary fructose intolerance; glucose–galactose malabsorption or sucrose–isomaltase insufficiency. Precautions: Maximum dose for severe liver impairment is 20mg; Long-term treatment; Pregnancy & lactation. Interactions: Ketoconazole; itraconazole: drugs metabolized by CYP3A4 (e.g. diazepam, citazapam, imipramine, clomipramine, phenytoin; warfarin; omeprazole; clarithromycin. Undesirable effects: Headache, abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation. Full local prescribing information is available upon request. APL: HK.NEX.004


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Gastro-oesophageal reflux-induced diseases (GERD) are commonly encountered gastro-intestinal disorders and classical symptoms include heartburn, acid regurgitation and atypical chest pain. Oesophageal manifestations and complications of GERD include erosive oesophagitis, oesophageal stricture, Barrett's oesophagus and oesophageal adenocarcinoma. The wide range of extra-oesophageal associations includes sleep disturbance, cough, laryngitis, laryngeal cancer, hoarseness, asthma, sinusitis and dental erosion. There is a perception that the prevalence of GERD is increasing in Asia and the prevalence assessed at two time-points in one city was rising in China and Singapore. Obesity, hiatus hernia, smoking and psychosocial factors like heavy workload, anxiety, divorce have been shown to be associated with GERD or heartburn. Although the prevalence of Barrett's oesophagus and adenocarcinoma of oesophagus is still low in HK Chinese, unexpectedly high figures were reported in Xi'an and Japan.

1. Pathophysiology of GERD
The contribution of hiatus hernia to GERD is well known. The hiatus hernia eliminates the contribution of the crural diaphragm to lower oesophageal sphincter function and thereby promotes gastro-oesophageal reflux, especially when intragastric pressure is increased due to distension or straining of the abdominal musculature. The most common cause of GERD in the West is an excessive exposure of the oesophagus to acid and pepsin during transient lower oesophageal sphincter relaxation (TLESR). These periods last for 10-30 seconds in normal persons to help to vent gas from the stomach but they are frequently associated with acid reflux in GERD patients. Once gastric acid is in the oesophagus, clearance mechanisms are activated to rapidly propel the acid back to the stomach and delayed gastric emptying are associated with reflux. A recent study from HK reported that impaired oesophageal acid clearance was the major mechanism of GERD.

2. Clinical approach to patients with classical GERD symptoms
Empiric trial of proton pump inhibitors (PPI) or a high dose PPI b.d. as a diagnostic test is widely recommended as the initial treatment. In a study of Chinese patients with GERD symptoms using high dose PPI for 2 weeks and a 50% reduction of symptoms as a positive response, the sensitivity and specificity of the high dose PPI test were reported to be 84% and 71% respectively, based on endoscopy or 24 hour pH study as gold standard. Endoscopy is usually reserved for refractory patients or those with alarm signs or symptoms such as anaemia, weight loss or dysphagia. An Asia consensus group recommended endoscopy for patients older than 35 years of age. Endoscopy allows identification of other benign or malignant diseases (e.g. oesophageal candidiasis), diagnosis of Barrett's oesophagus and classification of patients into those with mucosal disease (reflux oesophagitis) and those without (NERD). Those with mucosal disease required high dose PPI for at least 8 weeks as a recent study on low dose PPI for 8 weeks only led to complete mucosal healing in 48% of patients. Patients with NERD can be managed with step down or step up approach with PPI on a p.r.n. basis. Dietary advice and weight reduction may help some patients. Fortunately most patients with GERD in HK belong to mild erosive disease or NERD but stricture is occasionally encountered (Figure 1).
3. Extra-oesophageal manifestations of GERD

Convincing evidence exists linking each extra-oesophageal manifestation to reflux in some patients. However a causal relationship remains difficult to establish. The three most commonly investigated conditions are atypical chest pain, asthma and otolaryngeal manifestations. Data substantiating a significant beneficial effect of reflux treatment on symptoms are weak. Symptom relief may be incomplete for several reasons. First, these patients have heightened sensitivity to many different stimuli in the oesophagus. Consequently small amounts of acid could trigger these symptoms. Complete symptom control may be accomplished only by elimination of reflux which is rarely possible with even the best medical or surgical therapy. Secondly, these extra-oesophageal syndromes are usually multi-factorial with GERD as one of the several potential aggravating cofactors.

3a. Atypical chest pain

Individuals with acid reflux may also experience atypical chest pain, i.e. chest pain in patients for whom the results from cardiac work up were negative. It is believed to be one of the most common extra-oesophageal manifestations of acid reflux disease. In a local study based on telephone interview, 50% of patients with atypical chest pain had symptoms of GERD. A simple approach is to give high dose PPI for 1-2 weeks and a 50% reduction of symptoms is regarded as positive response. Endoscopy or 24 hour pH study or manometry are reserved for refractory cases.

3b. Asthma and chronic cough

Surveys suggested that 30-90% of asthmatic adults had reflux symptoms or abnormal oesophageal acid exposure and many studies showed an association between these two conditions. The value of identifying reflux in individual patients with asthma is now becoming more widely recognised. The recognition of reflux in asthma patients is important because some bronchodilators, which are often used to treat asthma symptoms, may themselves exacerbate reflux by contributing to relaxation of the lower oesophageal sphincter. Such commonplace asthma therapy may therefore indirectly exacerbate respiratory symptoms in some patients with asthma. Several mechanisms might link reflux with asthma. As well as reflux bronchoconstriction caused by the aspiration of refluxed stomach contents into the bronchi, small amount of acid regurgitation in the oesophagus may cause increased bronchial reactivity via a vagally transmitted reflex. The clinical benefits of PPI therapy on asthma patients in randomised trials are however not as great as expected. There is a significant benefit in improving symptoms and reducing asthma medications usage but no objective improvement in pulmonary function test. Those patients with nocturnal respiratory symptoms and GERD symptoms seem to respond best. A subset of patients responded dramatically to anti-reflux surgery with complete asthma resolution but the criteria for selection of patients for surgery is still unclear.

Gastro-oesophageal reflux may also be responsible for some cases of chronic cough but complete treatment response to medical treatment is rare in randomised controlled trials. The only strong support for the link comes from surgical studies that reported a significant resolution of symptoms in a subgroup of patients after laparoscopic fundoplication. Again, the criteria for selection of patients for surgery is not yet clear.

3c. Laryngeal signs and symptoms associated with gastro-oesophageal Reflux

Four to ten per cent of patients in the West presenting to otolaryngologists have reflux symptoms, and reflux is associated with hoarseness, chronic laryngitis, vocal cord ulceration and even carcinoma of the larynx. In a local study of 28 patients with throat symptoms like globus, throat discomfort, burping or cough lasting more than 1 month together with signs of laryngitis, 14% of patients showed objective evidence of acid reflux by pH monitoring. In another local study on 26 patients with globus, objective evidence of GERD was found in 30.8%. Similar to chronic cough, anti-reflux treatment only provides partial improvement in symptomatology and in some cases laryngoscopic appearance. There are probably many other co-factors in the aetiology of chronic laryngitis. Since pH study is not widely available, long term anti-reflux medication should only be continued for patients with both symptoms of GERD and/or signs of chronic laryngitis.

3d. Sleep disturbance

Insomnia, interrupted or poor quality sleep, is a common complication of gastro-oesophageal reflux. Recent data suggested that 50-80% of reflux patients might have disturbed sleep. Some cases appear to be associated with a nocturnal breathing disorder such as snoring or obstructive sleep apnoea. Many others are probably simply due to full or partial awakening in response to reflux-induced thoracic discomfort such as regurgitation or heartburn.

4. Management of refractory GERD patient

After a 4-8 week course of morning dose of PPI, 25-42% of patients may still have reflux symptoms. At this point, the physician should ensure the patient’s drug compliance and review the timing of the PPI dose (taken 30-60 minutes before meal). Endoscopy should be considered if not yet done. Some patients have predominantly nocturnal symptoms and one option includes changing the timing of the once daily dose from o.m. to before dinner. This would be based on intragastric pH data showing that overnight intragastric pH control is greater when once daily PPI is given before the evening meal, compared to the morning dose. Increasing the patient’s proton pump inhibitors to b.d. is another obvious and straightforward choice but the cost of drug will be high. Another choice would be to use an H2 blocker at bed time but tachyphylaxis occurred rapidly. Performing a 24 hour pH study may help to analyse the relationship between pH and symptoms. The result of 24 hr pH study of a patient with atypical chest pain who failed to respond to once daily PPI is shown in Figure 2. The overall 24 hr acid output is within normal limits in this patient but there is a good correlation between chest pain and acid reflux. The result suggests acid sensitive oesophagus and the patient responds to a higher dose of PPI given twice daily.

For patients who have refractory oesophagitis despite a b.d. dose of PPI, there are however several differential diagnosis such as drug-induced oesophagitis, skin disease associated oesophagitis, hypersecretory state
such as Zollinger-Ellison syndrome, genotypic differences and eosinophilic oesophagitis (diagnosed by biopsy). Endoscopy appearance of drug associated oesophagitis may range from one or more discrete ulcers to diffuse inflammation with exudates, or even stricture and pseudo-tumour formation. The most common site is the junction of the proximal and middle third of the oesophagus where peristalsis is weaker and where the aorta crosses the oesophagus. Common drugs include doxycycline and tetracycline, alendronate, aspirin and NSAID, potassium chloride, ascorbic acid, quinidine and ferrous sulphate. A variety of skin diseases may also cause oesophagitis such as lichen planus, pemphigus and pemphigoid. About 12-20% of Asians are said to be fast metabolisers of PPI. To date, all studies have been done with once daily dose of PPI and it is unknown if twice daily dosing may overcome the problem.

5. Barrett’s oesophagus and oesophageal adenocarcinoma

In some patients with abnormal gastro-oesophageal reflux, the oesophageal mucosa responds with the development of metaplastic columnar-specialised intestinal epithelium (Barrett’s oesophagus see Figure 3) an assumed risk factor for the development of oesophageal adenocarcinoma. In a recent American Society of Gastrointestinal Endoscopy guidelines\textsuperscript{15}, some of the recommendations for Barrett’s oesophagus are as follows:

A. Screening gastroscopy for Barrett’s oesophagus should be considered in selected patients with chronic long standing GERD. After a negative screening examination, further screening is not indicated.

B. For patients with established Barrett’s oesophagus, biopsy should be taken to look out for dysplasia. After 2 consecutive negative examinations for dysplasia in 1 year, further examination after 3 years is acceptable.

C. For patients with low grade dysplasia, further surveillance is recommended although the interval of surveillance is controversial.

D. For patients with high grade dysplasia, there is a significant risk for cancer and management options including frequent repeat endoscopy, oesophagectomy, endoscopic photodynamic therapy, endoscopic mucosal resection(EMR) should be discussed with patients.

In U.S, the pillcam (capsule endoscopy for the oesophagus) has been licensed to detect Barrett’s oesophagus without the need of invasive endoscopy but it’s not yet available in HK. Many new modalities like narrow band imaging (available in many hospitals already), magnifying endoscopy, chromoendoscopy and endo-microscopy have been developed to help to locate areas of suspicion of high grade dysplasia for biopsy and endoscopic treatment like mucosal resection or photodynamic therapy are options with variable success rate. Fortunately, the incidence of oesophageal adenocarcinoma is still low in HK but a rising trend is observed in Xi’an and Japan.
6. New advances in pH and impedance study
More recently wireless Bravo chip is available that can be affixed to the lower oesophagus. 48-72 hour pH data can be recorded via a portable data loggers and analysed by computerised devices. The Bravo system has been shown to improve patients' compliance as compared to conventional pH study and allows greater patient freedom to continue normal daily activities. Extended 48 hour pH study is useful as around 25% of cases may have excessive acid reflux in a single day only. However, early detachment within 16 hours resulting in shorter period of recording and technical failure (e.g. batteries) are not infrequently reported. Chest discomfort has also been reported after Bravo capsule attachment, possibly due to stimulated oesophageal contraction and occasionally requires removal of the chip. The device is also not widely available. The new multi-channel intraluminal impedance (MII) and pH study catheter can measure both acidic and non-acidic reflux at the same time and research is on-going to study its impact on clinical management.

7. Long term complication of PPI
Recently a retrospective data analysis 8 showed that long term PPI was associated with hip fracture. People over 50 years of age who took the drug for more than one year had a 44% increased risk of hip fracture. Taking PPI at higher dose and for longer periods pushed up the risk of hip fracture to 245%. The authors speculate that PPI stops gastric acid which is required for calcium absorption and they urge doctors to use the lowest effective dose of the drug. Other associations like Clostridium difficile associated diarrhoea and pneumonia have also been reported but the relationship remains speculative.

8. Endoscopic and surgical treatments for GERD
The Stretta procedure is an endoluminal radiofrequency energy delivery system for the treatment of GERD and obtained FDA approval in US since 2000. In a study up to 4 years17, 75% of patients treated with Stretta procedure required no or fewer medications than before at the end of assessment. There is also a favourable impact on lower oesophageal sphincter pressure, oesophageal acid reflux and symptom scores as well. Over four thousand procedures had been performed and unfortunately, a few perforations and two deaths were reported in the early post-marketing phase. Preliminary experience in Japan18 is promising and bigger studies in Asia are awaited. Other procedure like NDO plicator which can create a full thickness serosa-to-serosa apposition of the proximal cardia has also been approved in US but experience in Asia is limited.

Laparoscopic fundoplication has evolved as the surgical procedure of choice for patients with GERD. Although the durability of surgical treatment has been questioned, experienced surgeons achieve long term reflux cure rates of about 85-95%. Success with medical therapy is the only thing that predicts a successful surgical outcome. The only possible exception is in asthmatic patients where reduction of oral steroids was possible in a small series of Caucasian patients after surgery. Similar data from Asia are lacking. It is an option for patients who do not wish to take long term medications. Performance of bariatric surgery and fundoplication can also be done at the same time for patients with morbid obesity and GERD.

9. GERD and H. pylori
A negative correlation between GERD and H. pylori is observed in many Asian countries, suggesting a protective role of H. pylori against GERD. Although eradication of H. pylori may increase basal gastric acidity and reduce the efficacy of PPI therapy in some patients, the bacteria should still be eradicated to protect the patient from H. pylori associated gastric diseases.

References
Please read the article entitled “On Gastro-oesophageal Reflux-Induced Diseases” by Dr. Ambrose CP Kwan, and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded 1 CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 March 2008. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please choose the best answer:

1. Which of the following symptoms or condition is not associated with GERD:
   a. Chronic cough
   b. Hoarseness of voice
   c. H. pylori
   d. Dental erosions
   e. Globus

2. The pathophysiology of GERD may involve the following conditions except:
   a. Excessive exposure of the oesophagus to acid and pepsin during transient lower oesophageal sphincter relaxation
   b. Delayed oesophageal motility
   c. Hiatus hernia
   d. Accelerated gastric emptying
   e. Decreased lower oesophageal sphincter pressure

3. The followings are new investigations or treatment for GERD except:
   a. 48 hour wireless Bravo pH study
   b. Oesophageal capsule endoscopy
   c. 24 hour multi-channel intraluminal impedance for measurement of non acidic reflux
   d. MRI oesophagus
   e. Endoscopic photodynamic therapy for Barrett’s oesophagus with high grade dysplasia

4. Potential benefits of endoscopy in GERD patients include:
   a. Detect malignancy especially in patients with alarming signs and symptoms like anaemia, dysphagia or weight loss
   b. Assess the severity of reflux oesophagitis
   c. Diagnose Barrett’s oesophagus
   d. Narrow band imaging may detect areas of high grade dysplasia in patients with Barrett’s oesophagus
   e. All of the above

5. For GERD patients who do not respond to daily dose of proton pump inhibitors, the following actions are appropriate except:
   a. Combine two proton pump inhibitors (PPI)
   b. Add H2 blocker at nite time
   c. Consider 24 hr pH study or Bravo wireless 48 hour pH study
   d. Change the morning dose of PPI to 30 minutes before dinner
   e. Step up the dose of PPI to b.d.

6. The following drugs are associated with oesophagitis except:
   a. Alendronate
   b. Iron supplements
   c. Aspirin
   d. Potassium
   e. Calcium

7. The following statements on relationship between H. pylori and GERD is correct except:
   a. H. pylori infection is not associated with GERD.
   b. Eradication of H. pylori may increase basal gastric output in some patients with GERD.
   c. H. pylori should not be eradicated in patients with GERD.
   d. Eradication of H. pylori may affect the potency of PPI drugs.
   e. PPI therapy leads to migration of H. pylori from antrum to corpus.
8. The following statements on Barrett’s oesophagus are correct except:
   a. Barrett’s oesophagus is a highly-malignant condition
   b. Adenocarcinoma may arise from dysplastic lesion
   c. Barrett’s oesophagus is the replacement of normal squamous epithelium by metaplastic specialized columnar epithelium.
   d. Biopsy should be taken to assess the presence and degree of dysplasia.
   e. Chromo-endoscopy helps to identify areas of dysplasia

9. The following statements on treatment are correct except:
   a. Endoscopic therapy for GERD is well established in Asia.
   b. Results of laparoscopic fundoplication are best in patients who respond well to PPI therapy.
   c. Bariatric surgery and laparoscopic fundoplication can be done at the same time for patients with morbid obesity and GERD.
   d. Laparoscopic fundoplication offers an alternative form of therapy for patients who do not want to take long term medications.
   e. Long term durability of laparoscopic fundoplication has been questioned and a subset of patients may need to undergo re-operation or restart on PPI therapy few years later.

10. The following statements are correct except:
    a. Hip fracture is associated with long term PPI therapy
    b. Risk of hip fracture is higher with high dose PPI therapy.
    c. The incidence of adenocarcinoma of oesophagus is rising in HK.
    d. Fatty foods, coffee, chocolate, alcohol and smoking are provocative factors.
    e. The prevalence of GERD is rising in some Asian countries.

Please return the completed answer sheet to the Federation Secretariat on or before 31 March 2008 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

On Gastro-oesophageal Reflux-Induced Diseases

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Private Specialist in Gastroenterology and Hepatology

Name (block letters):__________________________ HKMA No.: ____________________________
HKID No.: ___ ___ - ___ ___ ___ ___ X X (x) Other Membership No. (please indicate): ____________________________
Contact Tel No.: ____________________________________________

Answers to February 2008 issue

Management of Youth Substance Users in General Practice Settings
Pentasa® is beneficial to UC and CD patients.

Its releasing mechanism is:

- independent from intestinal pH¹.
- less influenced by accelerated intestinal transit time².
- unaffected by food³.

References:
Inflammatory bowel disease (IBD), which encompasses Crohn's disease (CD) and ulcerative colitis (UC), is a spectrum of heterogeneous disorders with variable clinical manifestations and outcomes. It is thought to result from inappropriate and ongoing activation of the mucosal immune system driven by the presence of normal luminal flora. Although IBD manifests throughout all ethnic groups, there has been marked heterogeneity in its incidence and prevalence, presumably due to genetic and environmental factors. IBD is rare in the Chinese population, but its incidence is on the rise. This review will focus on the epidemiology of IBD in Hong Kong.

Little was known about IBD in Chinese before 1990s. Case report describing CD in our population was first published in 1994. In the past decade, incidence of CD has increased more than three-fold from 0.3 per 100,000 in 1989 to 1.0 per 100,000 in 2001. The rate of rise was greatest in the mid to late 1990s. The cause of this rise remains uncertain but may involve environmental changes associated with urbanisation and Westernisation of the living standards, culture and diet. Leong's study was conducted at the Gastroenterology outpatient clinic of the Prince of Wales Hospital. Eighty-five percent of patients were born in Hong Kong and 15% were emigrants from southern mainland China. The population consisted of middle-income earners, with a median monthly income slightly higher than the median income for the whole of Hong Kong and 45% of people had received a tertiary (university or technical college) education. It is believed that a higher socioeconomic class may be implicated in the development of IBD. The study was hospital-based, yet it reasonably reflected the regional population at that time because 94% of our population attended the public hospital system rather than to the private practice. The male to female ratio was 2.5:1. The mean age of diagnosis was 33.1 years with 78% of all patients presenting below the age of 40 years. The distribution of the age of onset was bimodal with the main peak of onset in the third decade, and a secondary peak in the sixth decade. The median time to diagnosis was nine months and the common symptoms at presentations were diarrhoea (65%), abdominal pain (65%), rectal bleeding (51%), and weight loss (45%). Extraintestinal manifestations were reported in 4% of CD patients upon diagnosis.

We have extended our former CD cohort and prospectively collected clinical data since 2001. Seventy-three out of the 109 (67%) patients started off with non stricturing, non penetrating disease (B1) according to the Montreal Classification (MC) which was a new classification developed by the international working party in 2005 for more precise categorisation of CD. In MC, perianal disease was no longer an independent criterion for B3 category but became a disease modifier based on the fact that perianal CD was recognised to have a different natural history from intestinal penetrating disease with respect to disease progression and outcome. The proportions of patients with stricturing (B2) and penetrating (B3) disease at diagnosis as determined by the MC were 30.3% and 2.8% respectively. CD behaviour changed significantly three years after diagnosis with an increase in the stricturing and penetrating phenotypes. The proportion of B3 increased from 2.8% to 14.3%, and B2 increased from 30.3% to 42.9% after ten years. In fact, phenotypic changes in CD also occurred in Chinese patients in the same way as Caucasian CD. The non-stricturing, non-penetrating phenotype had a tendency to progress into stricturing or penetrating disease, whereas stricturing diseases rarely developed penetrating phenotypes. This would support the concept that CD consists of a heterogeneous group of disorders that eventually result in a specific phenotypic complication. Fifty-four percent of patients in our CD cohort had ileocolonic disease (L3). Thirty-five percent and eleven percent of patients had colonic (L2) and terminal ileal disease (L1) respectively. Interestingly, there was more upper gastrointestinal tract disease (L4) as defined by any disease location proximal to the terminal ileum (excluding the mouth) in the Chinese CD patients. The figure was reported to be as high as 19%. Besides, the upper gastrointestinal location of CD often coexisted with L1 or L3 but never with the L2 location disease. This might be due to the Paneth cells being situated throughout the small bowel, which plays a vital role in secreting the inflammatory mediators for disease perpetuation. Disease location remained stable after ten years of follow up. The phenotype of CD patients reported by Lok and his group from the Tuen Mun Hospital was largely comparable to ours except that patients in the Lok’s cohort (n=27) did not have L4 disease which might be due to the small number of patients or possibilities of inadequate small bowel investigation. Thirty four patients (31.2%) in our CD cohort underwent major surgery during the follow up period and the Kaplan-Meier curve is shown in Figure 1. Stricturing (P=0.002; adjusted HR: 3.3; 95% CI: 1.5-7.0) and penetrating (P=0.03; adjusted HR: 5.8; 95% CI: 1.2-28.2) phenotypes according to the MC were predictive of the need for major surgery. Colonic disease was found to be protective against major surgery (P=0.02; HR: 0.3; 95% CI: 0.08 - 0.8). One
plausible explanation is that colonic CD presentations such as hematochezia, abdominal pain and diarrhoea, might drive our Chinese patients to an earlier presentation and treatment which may delay the onset of complications and subsequent surgery. In small bowel disease, symptoms might not be prominent until significant stricture develops. Age at diagnosis did not correlate with surgery in our cohort and neither was the history of smoking associated with surgery. Unlike the Caucasians, ever smoking was not a risk factor in the development of CD. The odds ratio (OR) of ever-smokers in the development of CD compared with age and sex matched healthy controls was only 1.02 (95% CI: 0.5-1.9). Interestingly, only 2 of our CD patients had a definite family history of CD and were of a father and son relationship. IBD is likely to be a polygenic disease of variable penetrance that requires a complex interaction of genes with the environment for disease manifestation. Vertical and horizontal familial clustering of IBD is reported up to 40% in Caucasians. This is in excess of the rate in Asian studies where the rate is 0-7%. The CARD15/NOD2 single nucleotide polymorphisms (SNPs) associated with CD have been confirmed in multiple Caucasian studies. Among CD patients, carrying at least one high-risk gene polymorphism increased slightly the risk for familial disease (OR: 1.5, 95% CI: 1.2 - 1.9), predicted the strictureting behaviour (OR: 1.9, 95% CI 1.6 - 2.3), and small bowel location of disease (OR 2.5, 95% CI 2.0 - 3.2). However, the prevalence of CARD15/NOD2 mutations in Chinese CD is negligible.16-17

The incidence of UC in our locality increased two-fold from 0.6 per 100,000 in 1986 to 1.2 per 100,000 in 2001. There is evidence that the incidence continues to increase (unpublished data). In our UC cohort in which more than 170 patients have been recruited, the median age of diagnosis was 37 years. Extensive colitis was found in 42.4% of patients at diagnosis, followed by left-sided colitis (29.7%) and proctitis (27.9%). However, ulcerative proctitis was reported to be the commonest disease phenotype (38.4%), followed by extensive colitis (35.6%) and left-sided colitis (26.0%) by the group from another regional hospital. Extra-intestinal manifestations occurred in 13.7% of patients. Four out of 73 (5.5%) patients underwent colectomy.

Our group conducted a study comparing the IBD-related knowledge, quality of life (QoL), and use of complementary and alternative medicines and therapies (CAMP) in Chinese and Caucasian IBD patients three years ago. The overall use of CAMT was similar in both groups (33% of Chinese and 37% of Caucasian patients) and similar for CD and UC. We found that the IBD knowledge score was higher in Caucasian than in Chinese IBD patients and was independent of education and occupation. Twenty-one percent of Chinese patients incorrectly identified their IBD type as compared to 0% in the Caucasian group. However, QoL was higher in the Chinese than the Caucasian group, but not significantly different after adjusting for disease activity inferring that health-related QoL is unlikely to be greatly influenced by disease-related knowledge or education. Treatment of IBD has undergone revolutionary changes over the past ten years since the emergence of biologics which might alter the course of the disease. Although the treatment of IBD is beyond the scope of this review, certainly there are lots of interests in the treatment response in using those new agents among our Chinese IBD patients. Clinical trials on the treatment of IBD in our population are scarce but definitely needed.

There were a number of factors which have impeded the study of IBD in our locality in the past including the absence of an IBD registry, physician unawareness, and attendance to traditional Chinese herbalists. Efforts must be made to overcome all those obstacles and hopefully, in the forthcoming years, we can establish a comprehensive regional if not national registry of IBD patients so that more meaningful epidemiology studies can be carried out to facilitate our local health policy planning and promotion and help define the natural history of the disease in our population.

Table 1. The Montreal classification of Crohn’s disease

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Location</th>
<th>Behaviour</th>
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<tbody>
<tr>
<td>A1 16 yr or younger</td>
<td>L1 Terminal ileum</td>
<td>B1# Non-structuring non-penetrating</td>
</tr>
<tr>
<td>A2 17-40 yr</td>
<td>L2 Colon</td>
<td>B2 stricturing</td>
</tr>
<tr>
<td>A3 Over 40 yr</td>
<td>L3 Ileocolon</td>
<td>B3 penetrating</td>
</tr>
<tr>
<td>L4* Upper gastrointestinal tract</td>
<td>B1p</td>
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*B1 category should be considered “interim” until a prespecified time has elapsed from the time of diagnosis.

Figure 1. Cumulative survival of CD patients free from major surgery upon 10 years of follow-up. Adopted from: Chow DK, Leong RW, Lai LH, et al. Changes in Crohn’s disease phenotype over time in the Chinese population: Validation of the Montreal Classification System. Inflamm Bowel Dis 2007 [Epub ahead of print]

References
Nonalcoholic fatty liver disease (NAFLD) has emerged as the most common chronic liver disease in affluent countries. Due to the adoption of Western diet and lifestyle, there is also an epidemic of NAFLD in Asia. In Japan and Indonesia, the prevalence of NAFLD is as high as 30%. In a population screening project in Shanghai, China, around 15% of the adults were also found to have NAFLD. Necroinflammation and fibrosis are common in Asian patients with NAFLD, and progression in fibrosis occurs in up to 50%. Progression to liver cirrhosis, liver failure and hepatocellular carcinoma has been reported. Besides, NAFLD patients have higher mortality than the general population, and the risk of cardiovascular diseases is doubled. Therefore, heightened awareness and proper management of this disease are important.

NAFLD has close relationship with the metabolic syndrome. Assessment of NAFLD patients should include both the evaluation of the liver condition as well as the associated features of metabolic syndrome. Healthy lifestyle remains the cornerstone for the management of NAFLD. Pharmacological treatment is reserved for patients with morbid obesity.

Clinical evaluation

Severity of liver disease

NAFLD can be roughly divided into simple steatosis and nonalcoholic steatohepatitis (NASH). Patients with simple steatosis run a benign course. On the other hand, patients with NASH tend to have progressive disease and increased mortality. One of the goals is to differentiate simple steatosis from more severe disease.

Traditionally, the assessment of NAFLD severity depends on histology. However, liver biopsy is an invasive and expensive procedure. It carries a small but definite risk of bleeding, pneumothorax, haemothorax, and puncture of adjacent organs. Although liver biopsy has been considered the gold standard, emerging data challenged this concept. In one study, biopsies were taken from both the right and left lobe of the liver during bariatric surgery. Concordance was only 53% for liver fibrosis between the two samples, and even poorer for most features of necroinflammation.

Due to the limitation of liver biopsy, there is strong interest in the development of non-invasive tests for liver fibrosis. They can be divided into serum biomarkers and elastography techniques.

The first development of non-invasive tests for liver fibrosis is to construct a formula including factors associated with fibrosis. The BARD, BARG, BAAT and HAIR scores were all developed for this purpose. The factors used in these scores include body mass index, age, AST/ALT ratio, ALT, diabetes, HbA1c, insulin resistance index, triglycerides and hypertension. Recently, a group of hepatologists from the United States, Europe and Australia reviewed the clinical data of 733 patients with biopsy-proven NAFLD and identified 6 factors independently associated with advanced liver fibrosis - age, body mass index, impaired fasting glucose or diabetes, AST/ALT ratio, platelet count and albumin. The NAFLD fibrosis score was constructed from these 6 parameters, and high and low cutoff values were selected. When the score is below the low cutoff point (< -1.455 from the study), the sensitivity and negative predictive value are 82% and 93%, respectively. When the score is above the high cutoff point (> 0.676), the specificity and positive predictive value are 98% and 90%, respectively.

There are a few limitations to these prediction models. Firstly, none of the parameters chosen is a direct measurement of fibrogenesis or fibrinolysis. Secondly, fibrogenesis and fibrinolysis are dynamic process, while both the score and the 'gold standard' of liver biopsy are taken as a snapshot. Thirdly, the 'gold standard' of liver biopsy is also limited by sampling bias and interobserver variability. Therefore, it is unlikely that these prediction models will ever achieve close to 100% accuracy.

Fibroscan is a one-dimensional transient elastography. It is a rapid and non-invasive method to measure the stiffness of the liver. Early data show that the accuracy of Fibroscan is at least as good in NAFLD patients as in patients with other chronic liver diseases. In 67 Japanese NAFLD patients, the sensitivity, specificity, positive and negative predictive values of Fibroscan to exclude stage 3 and 4 fibrosis (optimal cutoff 8 kPa) were 88%, 84%, 64% and 96%, respectively. However, it is important to note that the success rate of Fibroscan is lower in obese patients, who often harbour NAFLD. In patients with thick subcutaneous fat, Fibroscan may fail to acquire any reading because ultrasound waves cannot penetrate deep enough.

Metabolic syndrome

Apart from evaluating the severity of liver injury, clinicians should not ignore common comorbid illnesses. The Metabolic syndrome is closely associated with NAFLD. As a minimum, anthropometric measurements, blood pressure, fasting glucose and...
cards should be checked. Both the body mass index and waist circumference are used to assess the degree of obesity. In particular, waist circumference is a reflection of central obesity and is strongly associated with the risk of myocardial infarction.15 Moreover, people of different ethnicity develop complications of metabolic syndrome at different body mass indices.12 Therefore, the definition of obesity is different in different ethnic groups. In Chinese, normal waist circumference is below 90 cm in men and 80 cm in women.14 In Asia, people with body mass index above 23 kg/m² are considered increased risk and those above 27.5 kg/m² are considered high risk.15 The definition of metabolic syndrome by the International Diabetes Federation also takes ethnic differences into account (Table 1).14

The diagnosis of diabetes is made if the fasting plasma glucose is ≥7.0 mmol/l or the 2-hour plasma glucose is ≥11.1 mmol/l using a 75-gram oral glucose tolerance test.16 However, the American Diabetes Association discouraged performing oral glucose tolerance test because of cost and inconvenience. When oral glucose tolerance test was performed in NAFLD patients without history of diabetes, however, impaired glucose tolerance and diabetes were found in 29% and 33%, respectively.17 Moreover, post-challenge hyperglycaemia strongly predicted the presence of advanced liver fibrosis. According to the current guideline of the Asia-Pacific Working Party on NAFLD, oral glucose tolerance test should be considered in NAFLD patients.18, 19

Cardiovascular diseases
In addition to the association with metabolic syndrome, NAFLD also has close relationship with cardiovascular disease. Among 85 male volunteers in Italy, subjects with hepatic steatosis had significantly higher carotid intima-media thickness than those without steatosis (0.94±0.12 mm vs. 1.15±0.14 mm, p<0.001).20 The vasodilatory response of the brachial artery in response to ischaemia, a test of endothelial function, is also impaired in NAFLD patients.21 The strongest evidence for the association between NAFLD and cardiovascular disease came from the Valpolicella Heart Diabetes Study. Two thousand one hundred and three type 2 diabetes outpatients were followed up for a median of 6.5 years. After adjustment for sex, age, smoking, diabetes duration, HbA1c, LDL cholesterol and medications, NAFLD remained an independent factor predicting incident cardiovascular disease (hazard ratio 1.96, 95% confidence interval 1.4-2.7, p<0.001).7 Therefore, evaluation of NAFLD patients should include enquiry of symptoms and history of cardiovascular diseases. In positive cases, appropriate investigations should be arranged.

Treatment
Lifestyle management
Like most metabolic diseases such as type 2 diabetes and obesity, lifestyle modification remains the cornerstone of NAFLD treatment. In animal models, diets rich in olive oil, fish oil and fibre appear to improve hepatic steatosis.22-24 In one human study, 9 of 15 NASH patients undergoing 1 year of intense dietary intervention had histological improvement.25 The diet selected in that study was as follows: 40-45% of daily calories from carbohydrates with an emphasis on complex carbohydrates with fibre; 35-40% fat with emphasis on mono- and polyunsaturated fats; and 15-20% protein. It is however noteworthy that only 16 of 23 patients completed 12 months of dietary intervention, and only 15 had paired liver biopsies. This is a typical phenomenon in most lifestyle intervention studies. How one can achieve good compliance remains a major challenge to clinicians and allied health staff.

In another study involving 25 obese Japanese NAFLD subjects, diet restriction and exercise (walking or jogging) for 3 months resulted in improvement in metabolic parameters and liver histology.26 In 348 male employees with elevated ALT found during annual health checkup, weight loss and regular exercise were associated with ALT normalisation one year later.27

While there is ample observational data showing that diet and exercise are beneficial for NAFLD patients, it is difficult to recommend the optimal dose and type. Further studies are required.

Pharmacological treatment
Drug treatment of NASH is under intense investigation. The studied drugs are acting on various targets central to the pathogenesis of NASH: insulin resistance, lipid metabolism, oxidative stress, inflammation, fibrosis, etc.

The drugs that have attracted most attention are insulin sensitisers. Metformin was the first insulin sensitisers used to treat NASH. In a single-arm study involving 20 NASH patients, metformin 500 mg three times a day for 4 months resulted in ALT normalisation in 50% of the patients and improvement in insulin sensitivity.28 Subsequently, an open label, randomised trial showed that patients treated with metformin (2 g per day for 12 months) had a higher rate of ALT normalisation than controls.29 Metformin treatment also resulted in improvement in hepatic steatosis, inflammation and fibrosis. Unfortunately, only 17 patients receiving metformin had paired liver biopsies, and histological results of the control group were not presented.

Thiazolidinediones (pioglitazone and rosiglitazone) are another class of insulin sensitisers tested in NASH patients. In uncontrolled studies, both rosiglitazone and pioglitazone treatment for 12 months resulted in histological improvement in up to two-thirds of patients.30, 31 Recently, a randomised controlled trial on pioglitazone has been completed. Fifty-five NASH patients with impaired glucose tolerance or type 2 diabetes were randomised to receive pioglitazone 45 mg daily or placebo for 6 months.32 The pioglitazone group had decreased ALT levels, increased hepatic insulin sensitivity, and improved hepatic stLeanakos, ballooning necrosis and inflammation. However, the beneficial effect was not durable. When pioglitazone was stopped, serum ALT and total hepatic fat worsened again.33 Therefore, NASH patients will need long-term therapy if this drug is approved for this indication. Another problem of thiazolidinedione treatment is weight gain. In NASH patients treated with pioglitazone for 6 months, the average weight gain was 2.5 kg.34 When further tests were performed, increase in whole body fat was found to be the main cause of weight gain. This casts doubt on the long-term safety of the drug. Indeed, although several meta-analyses provided conflicting
data, there was concern over the cardiovascular safety during long-term rosiglitazone treatment.35

Since oxidative stress is pivotal in the pathogenesis of NASH, anti-oxidants have also been tested. In a double-blind, randomised controlled trial involving 45 NASH subjects, vitamin E and vitamin C resulted in some improvement in liver fibrosis, but not in ALT normalisation or necroinflammation.36

Ursodeoxycholic acid has been commonly used to treat primary biliary cirrhosis and other causes of cholestasis. In the largest clinical trial on NASH to date, 166 NASH patients were randomised to receive ursodeoxycholic acid or placebo for 2 years.37 However, ursodeoxycholic acid failed to demonstrate any superiority over placebo in all biochemical and histological assessments.

Other investigational therapies include phlebotomy, anti-inflammatory drugs (e.g. pentoxifylline, etanercept, infliximab, thalidomide, misoprostol), probiotics, betaine and pancaspase inhibitors. They need to be better evaluated in properly designed clinical trials.

Since NAFLD patients often have dyslipidaemia, one important question is whether lipid lowering drugs are safe in these patients. Among 68 NAFLD patients followed up for 10.3 to 16.3 years, statin use was found to be safe and not to cause histological deterioration.38 In another observational study involving 166 chronic hepatitis C patients on statin, 332 chronic hepatitis C patients not on statin, and 332 patients on statin but without hepatitis C infection, statin use in chronic hepatitis C patients was associated with mild-to-moderate ALT elevation, but not severe liver dysfunction.39 Recently, a randomised controlled trial included 326 patients with hypercholesterolaemia and chronic liver disease.40 NAFLD was present in 64% and chronic hepatitis C in 23%. The patients were randomised to receive pravastatin 80 mg daily or placebo for 36 weeks. Not surprisingly, pravastatin was effective in lowering the total cholesterol, LDL cholesterol and triglycerides. Moreover, fewer patients in the pravastatin group had doubling of ALT or ALT rising above 2 times the upper limit of normal than controls. All data support the safety of statin in patients with chronic liver disease. Current guideline also does not find close monitoring of liver function tests during statin therapy meaningful.19

Bariatric surgery
Bariatric surgery is effective in achieving weight reduction. Long-term mortality was significantly lowered in patients with morbid obesity undergoing bariatric surgery than those on usual medical care.41, 42 There was early concern that rapid weight loss might increase liver fibrosis in NAFLD patients. However, recent data showed that the risk is low if there was only modest weight loss and less malnutrition. Some observational studies also found improvement in steatosis, inflammation and fibrosis in NASH patients after bariatric surgery.

Conclusion
In summary, NAFLD is increasing in incidence. Although only a minority of NAFLD subjects eventually dies of liver complications, the absolute number is expected to be huge because the total number of NAFLD subjects is large. Serum biomarkers and transient elastography are potential non-invasive tests for liver fibrosis in NAFLD patients. Lifestyle modification is the most important management. Insulin sensitisers hold much promise as the pharmacological treatment of NASH, but long-term data are required. Statins and bariatric surgery are both safe in NAFLD patients, and should be provided if there is clinical indication.

Table 1. Metabolic syndrome definition by the International Diabetes Federation22

<table>
<thead>
<tr>
<th>Central obesity</th>
<th>Waist circumference (ethnicity specific)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plus any two:</td>
<td></td>
</tr>
<tr>
<td><strong>Raised triglycerides</strong></td>
<td>&gt;1.7 mmol/l Or specific treatment for this lipid abnormality</td>
</tr>
<tr>
<td><strong>Reduced HDL-cholesterol</strong></td>
<td>&lt;1.03 mmol/l in men &lt;1.29 mmol/l in women Or specific treatment for this lipid abnormality</td>
</tr>
<tr>
<td><strong>Raised blood pressure</strong></td>
<td>Systolic ≥130 mmHg Diastolic ≥ 85 mmHg Or treatment of previously diagnosed hypertension</td>
</tr>
<tr>
<td><strong>Raised fasting plasma glucose</strong></td>
<td>Fasting plasma glucose ≥ 5.6 mmol/l If above 5.6 mmol/l, oral glucose tolerance test is strongly recommended</td>
</tr>
</tbody>
</table>

Ethnicity specific definition of central obesity

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Waist circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Europeans</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥ 94 cm</td>
</tr>
<tr>
<td>Women</td>
<td>≥ 80 cm</td>
</tr>
<tr>
<td><strong>South Asians and Chinese</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥ 90 cm</td>
</tr>
<tr>
<td>Women</td>
<td>≥ 80 cm</td>
</tr>
<tr>
<td><strong>Japanese</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥ 85 cm</td>
</tr>
<tr>
<td>Women</td>
<td>≥ 90 cm</td>
</tr>
</tbody>
</table>

Figure 1. NAFLD is characterised by macrovesicular steatosis.
References

1. Amarapurkar DN, Hashimoto E, Lesmana LA, Sollano JD, Chen PJ, Goh KL. How common is non-alcoholic fatty liver disease in the Asia-Pacific region and are there local differences? J Gastroenterol Hepatol 2007;22:788-93.


Drug-induced Liver Injury: An Update

Dr. Tai-nin Chau

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Associate Consultant, Division of Gastroenterology and Hepatology, Department of Medicine and Geriatrics, United Christian Hospital, Hong Kong

Introduction

The liver is a major organ for metabolism of foreign substances and also functionally interposed between the site of resorption and the systemic circulation. These conditions render the liver not only the most important organ for detoxification of foreign substances but also a major target of their toxicity. More than 1000 drugs have been associated with idiosyncratic hepatotoxicity and drug-induced liver injury (DILI) is the main reason for removing approved medications from the market. Moreover, drug-induced hepatotoxicity contributes to more than half of the cases of acute liver failure, with paracetamol being the principal offending agent in western countries. In Sweden, hepatic injury due to drugs occurred in 2.3% of patients hospitalised for jaundice. However, the real incidence of DILI remains unknown because of the difficulty in establishing diagnosis and the low reporting frequency to the pharmacovigilance authorities. DILI represents a clinical challenge due to the large number of reported hepatotoxic drugs in current use, the broad spectrum of hepatic injuries by which it may manifest and the frequent absence of clinical findings that permit its diagnosis with certainty. Delay in the diagnosis of DILI may result in unnecessary extensive investigations and poor patient outcomes including acute liver failure and cirrhosis. The purpose of this review is to discuss the causality assessment of DILI in clinical practice and update the recent advances in the understanding of hepatotoxicity of some commonly used drugs and herbs, especially among patients with underlying liver disease.

Patterns of drug-induced liver injury

Hepatotoxicity may be predictable or unpredictable. Predictable reactions typically are dose-related and occur with short latency (within a few days) after some threshold for toxicity is reached. Paracetamol (acetaminophen) is a classic example. Conversely, idiosyncratic reactions occur with variable, sometimes prolonged latency (1 week to 1 year), with low incidence and, may be or may not be dose-related. On the basis of the alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels, the liver test abnormalities are classified into hepatocellular, cholestatic, and mixed patterns. Hepatocellular injury is characterised by the marked elevation of ALT level, usually preceding jaundice. However, the real incidence of DILI remains unknown because of the difficulty in establishing diagnosis and the low reporting frequency to the pharmacovigilance authorities. DILI represents a clinical challenge due to the large number of reported hepatotoxic drugs in current use, the broad spectrum of hepatic injuries by which it may manifest and the frequent absence of clinical findings that permit its diagnosis with certainty. Delay in the diagnosis of DILI may result in unnecessary extensive investigations and poor patient outcomes including acute liver failure and cirrhosis. The purpose of this review is to discuss the causality assessment of DILI in clinical practice and update the recent advances in the understanding of hepatotoxicity of some commonly used drugs and herbs, especially among patients with underlying liver disease.

Causality assessment of DILI

The presentation of DILI ranges from asymptomatic elevation of ALT level to acute liver failure and may mimic all forms of acute and chronic liver disease. High index of suspicion is paramount especially in patients using prescription or nonprescription medication or even dietary supplements. Other causes of liver disease must be ruled out. In appropriate clinical settings, sepsis-induced cholestasis and liver injury due to heart failure or "shock liver" should be considered. The hepatic dysfunction due to some non-drug causes is summarised in Table 1.

The Roussel Uclaf Causality Assessment Method (RUCAM) is the most widely-used methods for assessing non-organ-specific drug reaction to well-defined hepatic reactions. The RUCAM is based on 7 major criteria, namely (1) time to onset, (2) course of the reaction, (3) risk factors for the reaction, (4) assessing the role of concomitant therapies, (5) screening for non-drug-related causes, (6) weighing the information known about the DILI in question, and (7) confirmation of the reaction by positive rechallenge or in vitro assays. A causal relationship is graded as: excluded, unlikely, possible, probable, and highly probable. Liver biopsy is not considered as a diagnostic criterion for DILI as most of these patients present with a combination of acute and chronic liver disease. High index of suspicion is paramount especially in patients using prescription or nonprescription medication or even dietary supplements. Other causes of liver disease must be ruled out. In appropriate clinical settings, sepsis-induced cholestasis and liver injury due to heart failure or "shock liver" should be considered. The hepatic dysfunction due to some non-drug causes is summarised in Table 1.
Locality5 showed that Chinese subjects appeared to be similar to Caucasians. A pharmacokinetics study from our hospital found that the habit of drug usage between Chinese and Caucasians is different. Interestingly, paracetamol poisoning appears less common among Chinese and it is possibly due to the fact that Chinese are more likely to have a tendency to produce less toxic metabolites. However, further studies about the possible ethnic differences in paracetamol metabolism are needed before definitive conclusions can be made.

Common hepatotoxic agents

Paracetamol

The most commonly implicated drugs involved in acute liver injury and their disease patterns are summarised in Table 2. Paracetamol poisoning is the leading cause of drug-induced fulminant hepatitis in the United States. Traditionally, it is believed that a minimum of 7.5 - 10g of paracetamol is needed to produce hepatic necrosis in an adult. In the analysis of acute paracetamol-induced hepatotoxicity of the Acute Liver Failure Group in the United States4, a median dose of 24g was ingested with 44% of the cases due to an unintentional (suicidal) overdose. However, they found one patient who developed liver failure after taking only 1.2g of paracetamol, which is barely above a single therapeutic dose. It is possible that paracetamol (in non-toxic doses) may act as a cofactor with viral hepatitis or other medications to produce acute liver failure - a so-called 'dual pathology' scenario. Indeed, old age, the presence of underlying liver disease, poor nutritional status and the combination use of alcohol and opiates with paracetamol are all risk factors for paracetamol poisoning. Furthermore, long-term (about 1 year) exposure to paracetamol (3-4g daily) can also lead to chronic liver injury.

Interestingly, paracetamol poisoning appears less common among Chinese and it is possibly due to the different habit of drug usage between Chinese and Caucasians. A pharmacokinetics study from our locality5 showed that Chinese subjects appeared to be better protected against paracetamol hepatotoxicity by having more rapid absorption of paracetamol, as well as a tendency to produce less toxic metabolites. However, further studies about the possible ethnic differences in paracetamol metabolism are needed before definitive statements can be made.

Augmentin (amoxicillin/ clavulanic acid)

According to various registries and retrospective studies in European countries and the United States, antibiotics (including anti-tuberculosis drugs) are the most common agents causing DILI followed by non-steroidal anti-inflammatory drugs (NSAIDS), with diclofenac most often responsible for the DILI. It is worth mentioning that amoxicillin/clavulanic acid (augmentin) is the most frequently reported antibiotic associated with DILI. The estimated risk of symptomatic hepatitis due to augmentin is <1 in 100,000 persons exposed. Interestingly, age is found to be the most important determinant in the biochemical expression of augmentin-induced hepatotoxicity7. Patients younger than 55 years of age exhibit predominantly hepatocellular damage, which occurs at 1 week after exposure to the drug while cholestatic liver injury occurs mostly at 2-3 weeks and the mixed liver injury proportionally predominates after 3 weeks. In a prospective study by Andrade et al. in Spain, they reported that 13% (59/446) of their in- and out-patients suffering from acute DILI were due to augmentin and 6% of them developed acute liver failure or progressed to chronic liver disease and cirrhosis9. This brings into the question the generally-held opinion that the clinical outcome of hepatotoxicity caused by augmentin is invariably toward recovery.

Anti-tuberculosis drugs

Approximately 10-20% of patients receiving isoniazid will develop mild to moderate elevation of ALT and 

Table 1: Common non-drug causes of liver impairment

<table>
<thead>
<tr>
<th>Aetiologies</th>
<th>Diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral hepatitis</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A virus</td>
<td>HAV Ig M</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>HBc IgM and HBs Ag</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>Anti-HCV antibodies, HCV RNA</td>
</tr>
<tr>
<td>Hepatitis E virus</td>
<td>HEV IgM</td>
</tr>
<tr>
<td>Biliary tract diseases</td>
<td>Abdominal ultrasonography, ERCP, MRCP</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Gamma glutamyltransferase</td>
</tr>
<tr>
<td>Autoimmune diseases</td>
<td></td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Type 1: anti-smooth muscle</td>
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<td></td>
<td>antibodies, anti-nuclear factor</td>
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<tr>
<td></td>
<td>Type 2: anti-liver kidney-microsomal antibodies</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>Anti-mitochondrial antibodies</td>
</tr>
<tr>
<td>Haemodynamic disorders</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>Echocardiography</td>
</tr>
<tr>
<td>Ischaemia/hypoxia</td>
<td>Clinical scenario</td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
<td>Doppler ultrasound</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>Doppler ultrasound</td>
</tr>
<tr>
<td>Veno-occlusive disease</td>
<td>Liver biopsy</td>
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<tr>
<td>Metabolic/ genetic diseases</td>
<td></td>
</tr>
<tr>
<td>Wilson's disease</td>
<td>Diminished serum ceruloplasmin,</td>
</tr>
<tr>
<td></td>
<td>elevated urinary and serum copper</td>
</tr>
<tr>
<td>Haemochromatosis</td>
<td>Elevated iron saturation and ferritin levels</td>
</tr>
<tr>
<td>Sepsis-induced cholestasis</td>
<td>Sepsis work-up</td>
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</table>

Table 2: Commonly-reported drugs associated with drug induced liver injury (DILI)

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>diclofenac</td>
</tr>
<tr>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Naproxen</td>
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<tr>
<td>Antibiotics</td>
</tr>
<tr>
<td>Amoxicillin/ clavulanate (augmentin)</td>
</tr>
<tr>
<td>Flucloxacillin</td>
</tr>
<tr>
<td>Erythromycin</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Anti-tuberculosis drugs</td>
</tr>
<tr>
<td>Isoniazid, rifampicin, pyrazinamide</td>
</tr>
<tr>
<td>Anti-retroviral drugs (e.g. ritonavir)</td>
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<tr>
<td>Immunosuppressants</td>
</tr>
<tr>
<td>Azathioprine</td>
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<tr>
<td>Cyclophosphamide</td>
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<tr>
<td>Anti-arrhythmia drugs</td>
</tr>
<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>Anti-epileptics</td>
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<tr>
<td>Phenytoin</td>
</tr>
<tr>
<td>Carbamazepine</td>
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<tr>
<td>Valproic acid</td>
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<tr>
<td>Psychiatric drugs</td>
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<tr>
<td>Chlorpromazine</td>
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<td>Paroxetine</td>
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Anti-tuberculosis drugs

Approximately 10-20% of patients receiving isoniazid will develop mild to moderate elevation of ALT and about 0.1% develops clinical hepatitis. Slow acetylator status and genetic polymorphism of CYP2E1 have been identified as risk factors. The concomitant intake of other medications to produce acute liver failure-as o -

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risk of liver disease to 2-4%, which can be partly explained by an induction of CYP450 enzymes. There is a continuous interest in hepatitis B as a risk factor for anti-tuberculosis drugs-related hepatotoxicity. In 1990, a Taiwan study showed that 2.4% of patients treated with isoniazid, rifampicin and ethambutol developed symptomatic hepatitis of which, more than 35% were hepatitis B carriers and about half of them developed liver failure subsequently. In contrast, the mortality rate for non-hepatitis B carriers was less than 4%. Recent studies have shown that about 35-59% of hepatitis B carriers will develop abnormal liver function tests during anti-tuberculosis treatment and 25-50% of them are symptomatic.

Thus, it is recommended that a baseline clinical and laboratory evaluation, including liver function and hepatitis B surface antigen, should be performed before the start of anti-tuberculosis treatment. And patients should be taught to recognise symptoms of hepatitis and to report them promptly. Patients with risk factors for hepatotoxicity for example, those with preexisting liver diseases, the alcoholics, the elderly and malnourished should have their liver function monitored regularly. In fact, a study from India has shown that periodic biochemical monitoring in patients receiving anti-tuberculosis therapy allowed for early detection of hepatotoxicity at an early stage and reintroduction of therapy was successful in nearly all patients after initial recovery. According to the Consensus statement of Department of Health and Hospital Authority in Hong Kong in 2002, anti-tuberculosis treatment should be withheld if ALT > 3x of upper limit of normal (ULN) or bilirubin is greater than 2x ULN and non-hepatotoxic regimen (based on streptomycin, ethambutol and fluoroquinolone) may be reintroduced when ALT level <2x ULN. Potential hepatotoxic drugs can be reintroduced sequentially once liver function is normal. Whether anti-viral therapy for hepatitis B infection reduces the risk of developing anti-tuberculosis drug-related hepatotoxicity remains uncertain. We have reported a successful case of reintroduction of isoniazid and rifampicin after adding lamivudine in a chronic hepatitis B patient. Large-scale prospective studies are warranted to address this important clinical question.

Anti-diabetic drugs
Thiazolidinediones
Thiazolidinediones are insulin-sensitising agents used to treat diabetes mellitus through activation of the gamma isoform of the peroxisome proliferators-activated receptor (PPAR). Troglitazone, the first approved Thiazolidinediones, was withdrawn from the market in 2000 following 94 reported cases of liver failure. An idiosyncratic mechanism of toxicity was suggested based on the delayed onset of ALT elevation and a lack of dose effect. Rosiglitazone and pioglitazone were introduced into the market by the time troglitazone was withdrawn and both did not show an increased risk of ALT elevation in early clinical trials. Chalasani et al. also showed no difference in the rate of ALT elevation between diabetics with and without elevated baseline ALT level after taking rosiglitazone, suggesting that diabetics with elevated baseline ALT are not at a higher risk of hepatotoxicity from rosiglitazone. Indeed, a significant proportion of diabetic patients with abnormal liver tests at baseline had a decrease in ALT while taking rosiglitazone, which is probably due to the improvement in underlying fatty liver disease while discontinuing pioglitazone in patients with nonalcoholic steatohepatitis (NASH) may result in subsequent elevation in ALT levels and worsening of liver parenchymal inflammation. On the other hand, case reports of granulomatous hepatitis, cholestatic liver injury and fulminant liver failure due to rosiglitazone or pioglitazone have been reported. It is therefore advisable that thiazolidinediones should not be withheld in diabetics with minor liver dysfunction (ALT < 2.5x ULN) in the setting of NASH, especially given the potential beneficial effects, but it is prudent to monitor liver function tests during therapy.

Statin
Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are commonly used for hyperlipidaemia and form an important part of a preventative strategy against cardiovascular morbidity and mortality. Asymptomatic mild ALT elevation is a class effect of statins, and it does not indicate liver dysfunction. The incidence of ALT > 3x ULN associated with the use of statins is 0-3% and the rate has shown to be comparable with placebo in several trials. Clinically significant hepatotoxicity caused by statins remains extremely rare. Hepatocellular, cholestatic, and mixed patterns of liver injury have been reported in the literature. So far, there is no evidence to support routine monitoring of liver enzyme levels in patients receiving statins as it may result in high false-positive rates and unnecessary discontinuation of a drug that might be otherwise beneficial.

Although not evidence-based, current recommendations discourage the use of statins in patients with pre-existing liver disease. But this practice is problematic, because hyperlipidaemic patients have a significant prevalence of underlying NASH resulting in an elevated ALT level. Patients who have NASH would benefit from statins because of their heightened risk of cardiovascular disease. Furthermore studies showed that patients with compensated hepatitis C infection or primary biliary cirrhosis were not at higher risk for statin hepatotoxicity. Emerging data, in fact, suggest that statins are actually beneficial in patients who have underlying liver disease. Thus, the Liver Expert Panel has made recommendations to the National Lipid Association that the presence of chronic liver disease and Child’s A cirrhosis should not be considered as a contraindication for statin use, and that the current evidence supports the use of statins to treat hyperlipidaemia in patients with NASH.

Herbal products
Herbal medicine is widely used for the treatment of many common diseases in western countries as well as in Hong Kong. About 10% of adults in Hong Kong have consulted traditional Chinese medicine doctors and
13.5% have been using traditional Chinese medicine drugs. In a local survey, 32% of chronic hepatitis B patients have received traditional Chinese medicine. Herbal medicine is usually believed as ‘natural’, harmless and without side-effects. However, a German study showed that 0.9% of patients on Chinese herbal medicine had a more than 2-fold elevation of ALT level. A prospective study from Queen Mary Hospital showed that 7 of 45 (15.6%) chronic hepatitis B patients developed liver dysfunction attributable to traditional Chinese medicine and 3 of them developed liver failure. The Chinese herbal medicine had a more than 2-fold elevation of ALT level. The common Chinese herbal medicines with potential hepatotoxicity are listed in Table 3. Diagnosing herb-induced hepatotoxicity is a major challenge to clinicians and sometimes impossible in some cases. Many patients often do not disclose the use of herbal medicines spontaneously and physicians should make specific inquiries about the use of herbal medicine. Many herbal formulae contain a list of different herbs of different dosages which make us difficult to impute the toxicity to a single herb. The amount of the herbs taken by patients, the possible interactions between different herbs and western medicines, the synergistic hepatotoxicity of herbal preparations, and risk factors of patients have to be considered. Additional problems with formulation of herbal medicines include botanical misidentification, product contamination or adulteration, and mislabelling and variability in the collection and extraction processes.

Table 3. Some common Chinese herbal medicine associated with hepatic dysfunction

<table>
<thead>
<tr>
<th>Chinese Name</th>
<th>Plant/Component</th>
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<tr>
<td>千里光</td>
<td>Herba Seneconis Scandentis</td>
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<tr>
<td>石䉙子</td>
<td>Fructus Toosendan</td>
</tr>
<tr>
<td>五倍子</td>
<td>Galla Chinensis</td>
</tr>
<tr>
<td>及已</td>
<td>Radix Chloranthi Serrati</td>
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<tr>
<td>天花粉</td>
<td>Radix Trichosanthis</td>
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<td>石榴皮</td>
<td>Pericarpium granati</td>
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<tr>
<td>鱼膽</td>
<td>Fish gallbladder</td>
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<tr>
<td>黃藥子</td>
<td>Tuber Dioscoreae Bulbiferae</td>
</tr>
<tr>
<td>雷公藤</td>
<td>Tripterygium wilfordii Hook</td>
</tr>
<tr>
<td>蒼耳子</td>
<td>Fructus Xanthii</td>
</tr>
<tr>
<td>喜樹</td>
<td>Fructus seu Radix Camptothecae Acuminatae</td>
</tr>
<tr>
<td>龜蛇粉 (川足)</td>
<td>Dried centipede</td>
</tr>
<tr>
<td>石蠟</td>
<td>Germander (Teucrium chamaedrys)</td>
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<td>金不換</td>
<td>Lycopodium serratum</td>
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<tr>
<td>麓頭</td>
<td>Ephedra sinica</td>
</tr>
<tr>
<td>小葉黃楊 (柴胡, 半夏, 白芷, 黃芩, 大黃, 人蔘, 甘草)</td>
<td>Xiao-chai-hu-tang (Bupleurum falcatum, Scutellaria baicalensis, etc.)</td>
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<tr>
<td>胡薄荷油</td>
<td>Pennyroyal oil (pulegone)</td>
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<tr>
<td>虎杖</td>
<td>Rhizoma Polygonyi Cuspidati</td>
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Conclusions

Drug-induced liver diseases mimic various forms of liver injury that range in severity from transient, asymptomatic elevation in ALT levels to fulminant liver failure. The diagnosis of DILI is predicated on the exclusion of other possible causes and on the identification of a clinical signature that consists of the pattern of liver test abnormality, the duration of latency to symptomatic presentation, and the response to drug withdrawal. Administration of drugs in patients with underlying liver disease involves a balanced assessment of risk-benefit ratios that may favour judicious use when clear indications are present, as in the case of statins. Further studies are needed to provide better understanding of the pathogenesis and susceptibility to drug-induced liver injury which may in turn facilitate the prediction of human toxicity and provide better biomarkers for diagnosing DILI.

References

Upper Gastrointestinal Bleeding During Anti-platelet Therapy

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Introduction

Anti-platelet therapy is effective in reducing the incidence of cerebrovascular accident, myocardial infarction and death from vascular causes in individuals with symptomatic atherothrombotic diseases.1 Low-dose aspirin is most commonly used for the secondary prevention of vascular events. However, its use is frequently associated with adverse gastrointestinal events, which ranged from mild dyspepsia (31%) to life-threatening bleeding or perforation from peptic ulcer (3.1%) over a study period of 4 years in the UK Transient Ischaemic Attack study.2 The elderly are regarded as a high-risk group. Clinically evident gastrointestinal bleeding occurred in 3% of elderly patients (70 years of age or older) receiving 100 mg of daily aspirin for 12 months.3 Clopidogrel (Plavix, Bristol-Myers Squibb Co.), another form of antiplatelet agent, has been approved by the Food and Drug Administration for use in secondary prevention of heart attacks and stroke.4 Clopidogrel, a thienopyridine derivative similar to ticlopidine inhibits platelet aggregation through a different mechanism from aspirin. Aspirin inhibits platelet aggregation by irreversibly blocking the enzyme cyclooxygenase. This is essential for the synthesis of thromboxane A2, a substance which causes vasoconstriction and amplifies the platelet activation process leading to platelet aggregation.5 By contrast, the thienopyridines inhibit platelet aggregation by irreversibly inhibiting the binding of adenosine diphosphate, a substance released from platelets during activation that amplifies the aggregation process. Thienopyridines do not impair the prostaglandin-dependent mucosal protective and ulcer healing mechanism, which is a side effect of aspirin.6

This review aims to investigate the role of clopidogrel in patients with a history of peptic ulcers or erosions and to examine upper gastrointestinal bleeding in patients receiving aspirin and clopidogrel co-therapy. Since long-term proton pump inhibitors are widely prescribed in the prevention of antiplatelet induced peptic ulcer complications, its long-term safety is briefly reviewed.

Clopidogrel alone in patients with history of bleeding peptic ulcer is unsafe

The clinical efficacy of clopidogrel in secondary prevention of coronary heart disease, peripheral vascular disease and ischaemic stroke is demonstrated to be marginally more effective than aspirin in a randomised controlled clinical trial [Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE)].7 The incidence of severe adverse upper gastrointestinal (GI) events was significantly lower for clopidogrel than aspirin (dyspepsia 0.97% versus 1.22%; p<0.05; severe GI haemorrhage 0.52% versus 0.72%; p<0.05). Therefore, clopidogrel is safer than aspirin in average-risk patients, although the number needed to be treated by clopidogrel to prevent one excess aspirin-induced severe GI bleeding was 500. Indeed, in healthy volunteers without endoscopic gastroduodenal disease at baseline, an 8-day course with clopidogrel (75 mg/day), in contrast to aspirin (325 mg/day), did not induce any erosions on repeat endoscopic examination.8

Since clopidogrel causes less GI bleeding than aspirin in average-risk patients, can clopidogrel replace aspirin in higher risk patients with peptic ulcer disease? In patients with active bleeding peptic ulcer, clopidogrel is definitely contraindicated.9 In patients with previous peptic ulcer, there have been one retrospective study and two prospective randomised controlled studies on the safety of replacement of aspirin by clopidogrel therapy. In a retrospective study (n=70), 9 (12%) patients developed gastrointestinal bleeding after clopidogrel therapy for a median follow-up of one year. Clopidogrel-associated GI bleeding was significantly more common in patients with a history of GI bleeding associated with the use of aspirin or H. pylori infection than in those without (22% versus. 0%, p=0.007). Previous history of GI bleeding was the only independent predictor of clopidogrel-associated rebleeding. All except one lesion found during rebleeding were identical to the previous lesions, suggesting that impaired haemostasis from clopidogrel therapy might precipitate bleeding from an unhealed or relapsed ulcer. However, rebleeding occurred in none of the patients receiving a proton pump inhibitor. Hence, clopidogrel treatment alone may not be safe in high-risk patients and concomitant long-term proton pump inhibitor prophylaxis should be considered in this setting. Subsequently, this was followed by two randomised controlled studies. The first study recruited patients who took aspirin to prevent vascular events and presented with ulcer bleeding (n=320).10 After ulcer healing and eradication of H. pylori (if infected), patients were randomised to receive either clopidogrel (75 mg daily) plus placebo or aspirin (80 mg daily) plus esomeprazole (20 mg twice daily) for 12 months. The cumulative incidence of recurrent bleeding was significantly higher in the clopidogrel group (8.6%), as compared to the aspirin plus esomeprazole group (0.7%).

References

Continuation of aspirin with proton pump inhibitor or conversion to clopidogrel with proton pump inhibitor is safe in moderately severe peptic ulcer disease

In patients with low-dose aspirin induced symptomatic peptic ulceration, what is the best initial treatment? By analogy with trials using full-dose conventional non-steroidal anti-inflammatory drugs, our current practice is to prescribe a proton pump inhibitor while continuing aspirin in patients without severe gastrointestinal bleeding. Although discontinuation of aspirin during the period of ulcer healing may offer a theoretical advantage, there is always a potential of precipitating an ischaemic vascular event, particularly in high-risk patients with unstable angina.

In a randomised controlled study, patients (n=129) with aspirin induced peptic ulcer disease treated with omeprazole (20mg/day) were randomised to receive clopidogrel or to continue with low-dose aspirin. Before randomisation, around 40% of patients in each group had minor gastrointestinal bleeding. These patients had small ulcers without adherent clot or visible vessels or patients with moderately severe gastro-duodenitis. Clopidogrel and aspirin were re-started after 0.86 and 0.44 days after upper endoscopy respectively. The result of this study demonstrated the incidence of unhealed ulcers or erosions at the 8th week was similar in both groups. Furthermore, thrombolytics was used in 6-7% of patients in each group.

Adverse impact of gastrointestinal bleeding in acute coronary syndrome

The efficacy of a combination of aspirin, clopidogrel and anticoagulation has been established in patients with acute coronary syndrome. The American College of Cardiology / American Heart Association guidelines recommend the use of unfractionated or low molecular weight heparin in addition to aspirin and clopidogrel for the management of unstable angina or non-ST elevation myocardial infarction (class I indication). Enoxaparin is preferable to unfractionated heparin in the absence of renal failure and if coronary artery bypass graft surgery is not planned within 24 hours.

The major adverse event of the combination of heparin, aspirin and clopidogrel is bleeding, particularly from the gastrointestinal tract. However, information on gastrointestinal bleeding is scarce. The incidence rate of bleeding can only be inferred from The Clopidogrel in Unstable Angina To Prevent Recurrent Events Trial. This randomised controlled study primarily examined the efficacy and safety of the addition of clopidogrel to aspirin in patients with acute coronary syndrome over a mean follow-up of 9 months. Anticoagulation was used in ~70% of patients in both groups. Furthermore, thrombolytics was used in 1-2% of patients and glycoprotein IIb/IIIa receptor antagonist was used in 6-7% of patients in each group. Overall, the rate of early major bleeding within 30 days after randomisation was significantly higher in the combination group than the aspirin alone group (2.0% versus 1.5%). The most frequent site of excess major bleeding episodes was the gastrointestinal tract followed by bleeding at arterial puncture sites.

Recently, the adverse impact of bleeding in acute coronary syndrome has been recognised. In the first study, the association between bleeding and death or ischaemic events in 34 146 patients with acute coronary syndrome enrolled in three registries was examined. Patients with major bleeding were older, more often had diabetes or a history of stroke, had a lower blood pressure and higher serum creatinine and more often had ST-segment changes on the presenting ECG. Patients with major bleeding had a 5-fold-increase in mortality rate at 30-day (12.8% versus 2.5%; p=0.0001) and a 1.5-fold-increase in mortality rate between 30 days and 6 months (4.6% versus 2.9%; p=0.002). The severity of bleeding was associated with mortality (minor less than major less than life-threatening; P for trend =0.0009). In the second study, gastrointestinal bleeding after percutaneous coronary intervention for acute myocardial infarction in the Primary Angioplasty in Myocardial Infarction trials involving 3,130 patients was evaluated. 2.3% developed gastrointestinal bleeding, which was more likely to occur in elderly patients. Gastrointestinal bleeding was independently associated with a prolonged hospital stay (6.4 versus 12.6 days p=0.0001) and greater in-hospital mortality (2.8% versus 10%, p=0.0046) and 6-month mortality (4.6% versus 14%, p=0.0016). This difference may be partly accounted by the premature termination of anti-platelet therapy during bleeding. In fact, premature discontinuation of clopidogrel therapy 30 days after drug-eluting stent placement for acute myocardial infarction resulted in more deaths during the next 11 months (7.5% versus 0.7%, p=0.0001; adjusted hazard ratio 9.0; 95% confidence interval 1.3 to 60.6). Therefore, evaluation of strategies to reduce bleeding and thereby improve clinical outcomes is urgently needed.
Prevention of upper gastrointestinal bleeding in acute coronary syndrome

What is the strategy to prevent gastrointestinal bleeding during aspirin and clopidogrel co-therapy? Unfortunately, the information is sparse. Currently, there has been no randomised controlled study published in the English literature. There are only two cohort studies.

In the first case-control study20, upper gastrointestinal bleeding in the 30 days following PCI for stable angina and acute coronary syndromes was evaluated. The incidence of upper gastrointestinal bleeding following PCI was 1.2% (70 of 5,673 patients). The risk factors were primary PCI (odds ratio 27.80, P < 0.001), cardiac arrest (odds ratio 6.17, P = 0.003), inotropic requirement (odds ratio 5.85, P = 0.001), thienopyridine use before PCI (odds ratio 2.40, P = 0.02), and advanced age (odds ratio 1.08, P < 0.001). Endoscopy provided therapeutic intervention in 33% of patients with no serious complications during endoscopy. Prescription of proton pump inhibitors (odds ratio 0.08, P = 0.002) was accompanied with a reduced risk. The 30-day mortality for patients with upper gastrointestinal bleeding was significantly higher (11.9% versus 0.5%, P = 0.001).

In the second study21, a cohort of 666 patients receiving a combination of aspirin, clopidogrel and enoxaparin was evaluated for upper gastrointestinal bleeding at the 7th day after stopping combination therapy. Gastrointestinal bleeding occurred in 2.7% patients. The age adjusted odds ratio (95% confidence interval) for gastrointestinal bleeding was 5.07 (1.31-16.58) for previous peptic ulcer and 21.41 (2.56-146.68) for cardiogenic shock. Co-prescription of proton pump inhibitors could reduce the risk [odds ratio 0.07 (0.01-0.27)]. A prospective randomised controlled study to evaluate the efficacy of proton pump inhibitors is warranted.

Safety of long-term proton pump inhibitors

The safety of long-term administration of proton pump inhibitors in humans is not totally clear yet. In general, long-term PPI therapy appears to be safe in humans. However, gastric cancer did occur in rats receiving high dose PPI therapy. Enterochromaffin-like cell carcinoids developed in 20% of rats after life long high dose omeprazole therapy22. Gastric carcinoma developed in 90% of rats with duodenogastric reflux after one year of omeprazole therapy23. Fortunately, these have not been observed in humans. Lambers et al reported that only argyrophil cell hyperplasia secondary to PPI- induced hypergastrinemia developed in 19% patients receiving high dose omeprazole (40 mg - 60 mg daily) for 10 years24. There was no gastric atrophy, intestinal metaplasia, argyrophil cell dysplasia or neoplasia. Despite this assurance, there have been reports of development of gastric fundic gland polyps and hyperplastic polyps in both adults and children receiving long-term omeprazole therapy, although their natural history and long-term clinical significance is currently unknown15,22.

Conclusion

In summary, in patients with no history of peptic ulcer disease or gastrointestinal bleeding, clopidogrel appears to be safer than aspirin. However, the cost-effectiveness should be analysed since 500 patients need to be treated with clopidogrel to prevent only one aspirin-induced severe gastrointestinal bleeding. In patients with dyspeptic or moderately severe bleeding peptic ulcers, both approaches of early conversion to clopidogrel or continuation of aspirin are safe if the patients are maintained by proton pump inhibitors. Future studies are required to address anti-platelet strategies in very high risk bleeding peptic ulcers, particularly requiring endoscopic haemostasis. On the other hand, long-term administration of clopidogrel alone, without proton pump inhibitor prophylaxis is unsafe in patients with history of bleeding peptic ulcer. In patients with acute coronary syndrome, the addition of clopidogrel to standard aspirin therapy reduces the rate of major adverse cardiovascular events but is associated with gastrointestinal bleeding. Bleeding is associated with adverse cardiovascular outcome. The co-prescription of proton pump inhibitors appears to reduce the risk. Long-term administration of proton pump inhibitors appears to be safe in humans. Further prospective studies for the prevention and management of gastrointestinal bleeding during aspirin and clopidogrel ± antiocoagulation therapy and the role of H2-receptor antagonist in the prevention of antiplatelet drug-induced peptic ulcer disease are warranted.

References

Clinical Quiz

Dr. Ka-kin Wong

MBBS, FRCR
Queen Mary Hospital

Clinical Information:
Two-month old baby boy presented with poor oral feeding and bilious vomiting.

Questions:
What were the radiological findings and diagnosis?

(See P.37 for answers)
With Zeffix™, every milestone is a step in the right direction.

Zeffix™ is the only oral antiviral proven to reduce disease progression.†

† Zeffix is an investigational drug. The clinical benefit of Zeffix in the treatment of chronic hepatitis B remains to be established. Zeffix is not approved for use in the United States or any other country.
Risk Stratification for Patients with Chronic Hepatitis B

Dr. Morris Sherman
Department of Medicine, The University of Toronto, Canada

Although the liver diseases that predispose to hepatocellular carcinoma (HCC) and liver failure are well known, not everyone with these diseases will develop these outcomes. Ideally, if it could be predicted accurately who would develop these bad outcomes, treatment strategies to prevent cirrhosis and HCC could be instituted, and screening programmes for HCC could be targeted to the appropriate population.

Among hepatitis B carriers a number of factors have been identified that confer added risk of cirrhosis and HCC. HBV DNA concentration is the best predictor of risk of HCC and cirrhosis. As HBV DNA concentration increases, risk of HCC also increases, with a threshold of risk starting to rise at an HBV DNA concentration somewhere between 104 and 105 copies/ml. This has been shown in several large scale studies. Elevated ALT is also a predictor of increased risk of cirrhosis and HCC, but not as strong a predictor as HBV DNA concentration. Other factors include advancing age, presence of fibrosis on biopsy, hepatitis B genotype C vs genotype B and genotype D vs genotype A. A risk function nomogram providing 5 and 10 year risk for HCC has been developed.

Among cirrhotic patients other factors imply increased risk of HCC or liver failure. These include ongoing viral replication, falling platelet count, and presence on biopsy of several histological markers, such as large cell change, and asymmetric regeneration.

Treatment Goals: Can Chronic Hepatitis B be Cured?

Prof. Ching-lung Lai
Department of Medicine, The University of Hong Kong, Hong Kong

The ultimate goals for the treatment of chronic hepatitis B is to prevent (or at least delay) the development of cirrhosis complications and hepatocellular carcinoma. It has been shown that prolonged suppression of viral replication with lamivudine can decrease cirrhosis complications and HCC in both patients with cirrhosis and patients without cirrhosis. However, especially in patients who acquire the infection early in life, i.e., most Asian, Mediterranean or African carriers, disease does progress, and complications of cirrhosis and HCC do occur, after HBeAg seroconversion, with HBV DNA levels at relatively low levels (>104 copies/mL or >2000 IU/mL) and ALT levels between 0.5-2 times the upper limit of normal (ULN). Even after clearance of hepatitis B surface antigen (HBSAg), the risk of HCC is not decreased if the patients only lose HBSAg after the age of 50.

The ideal treatment endpoint is HBeAg seroconversion together with permanent suppression of HBV DNA to below PCR detectability and normalisation of ALT levels to <0.5 ULN. As to whether one can consider this as a “cure” for the disease, the fact that patients with HBSAg seroclearance can develop HCC seems to imply a negative answer. However, whether further clearance of covalently closed circular (ccc) HBV DNA in hepatocytes can be considered as a cure has yet to be investigated. That ccc DNA can be lowered with nucleos(t)ide analogue treatment has been documented.

References

Management of HBV drug resistance

Prof. Fabien Zoulim

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Despite the recent progress in antiviral therapy of chronic hepatitis B, clinical experience has shown that antiviral drug resistance is inevitable with the administration of nucleoside analog monotherapy. Several antivirals have now been approved because their antiviral efficacy is associated with an improved outcome of the liver disease during the follow-up period. The long-term persistence of the viral genome in infected cells and the high rate of spontaneous mutation is the basis for the selection of HBV mutants that are resistant to polymerase inhibitors. Selection of antiviral-resistant mutations leads to a rise in viral load and progression of liver disease. The incidence of antiviral resistance depends on the potency and genetic barrier to resistance of the antiviral drug, highlighting the importance of the choice of first line therapy. The...
determination of cross-resistance profile of each drug has allowed the design of rescue therapy for patients with virologic breakthrough. Early diagnosis and treatment intervention allow the majority of patients to maintain in clinical remission despite the occurrence of drug resistance. Clinical studies are ongoing to determine the best strategy to prevent or delay antiviral drug resistance and its impact on liver disease.

References

Impact of HBV Genotypes and Mutants in HCC
Prof. Masashi Mizokami
Department of Clinical Molecular Informativic Medicine, Nagoya City University, Japan

420 million people are estimated to be suffering from chronic infection of hepatitis B virus (HBV) and HBV has been a public health problem worldwide, since it was first identified in 1967. Recent studies showed eight genotypes, A-H, of HBV are distinguished by a divergence >8%. Molecular evolutionary analysis in the entire genomic sequence showed association with anthropologic and human migration. One of the most important findings in HBV genotypes is the distinct geographic distributions and their association with clinical manifestations of disease in hosts. Genotype A and D are major genotypes in Europe and genotype A has been reported to be associated with chronic liver disease less frequently than genotype D. Nevertheless, subgenotype A1(Aa), mainly in Africa, is suspected to be associated with high prevalence of hepatocellular carcinoma (HCC) with specific mutation in the precore (PC) region which is called Kozack mutation in South Africa. Genotype E is reported to be strongly associated with progression to HBV carrier state during childhood in West Africa and genotype F is localised in the New World. There is still unclear association between HCC and specific mutations of genotype E and F. Recently identified genotype G always co-infects with genotype A and is incapable of the processing of HBcAg. The high frequency of the recombination with other genotypes is still unclear in clinical significance. In East Asia, genotype B and C are predominant and genotype C has a higher disease-inducing capacity than genotype B with high positivity of HBeAg and mutations in basic core promoter (BCP), CP, and X region. Moreover, genotype B is classified into 2 subgenotypes, B1(Bj) and B2(Ba). Ba is located in Asian countries except Japan and recombined with genotype C in the core and BCP region. Interestingly, determination of cross-resistance profile of each drug has allowed the design of rescue therapy for patients with virologic breakthrough. Early diagnosis and treatment intervention allow the majority of patients to be maintained in clinical remission despite the occurrence of drug resistance. Clinical studies are ongoing to determine the best strategy to prevent or delay antiviral drug resistance and its impact on liver disease. Ba is strongly associated with HCC among the young generation. These data indicated that clinical differences among HBV genotypes would be attributable to the infected hosts and genome structure of HBV genotypes. To investigate these differences, we developed HBV transfection system using 1.24-fold HBV genome constructs belonging to HBV genotypes, AA, A2(Ae), BJ, BA, C and D and Huh7 cells for in vitro test, and severe combined immunodeficient mice transgenic for urokinase-type plasminogen activator transduced with human hepatocyte (chimeric mice) for in vivo test. HBV DNA levels in cell lysates of Huh 7 cells were the highest for C, followed by BJ, BA, and AE (P < 0.01) and the lowest by AA (P < 0.01), whereas in culture media, they were the highest for BJ, distantly followed by BA, C and D (P < 0.01), and further by AE and AA (P < 0.01). HBV Core protein was about 3-fold higher for D than AE and AA. Cellular retention in Huh 7 cells was higher for C and BA than other genotypes. HBsAg was most abundant for AE followed by AA, BA, C, and D. The highest 2C/2A in vivo test. HBV DNA levels expressed in the chimeric mice were higher for C than AE by 2 logs at 4 to 7 weeks postinoculation. In conclusion, virologic differences in HBV genotypes were demonstrated both in tissue culture and the chimeric mice. These differences can explain the different clinical manifestations of HBV infections with distinct genotypes in the host.

Local Ablative Treatment of HCC
Prof. Ronnie Poon
Department of Surgery, The University of Hong Kong, Hong Kong

Local ablative treatment is a potentially curative treatment for hepatocellular carcinoma (HCC) not amenable to resection or liver transplantation. Percutaneous ethanol injection (PEI) used to be the main modality of local ablative therapy. In recent years, various thermal ablative therapies such as radiofrequency ablation (RFA), microwave and high intensity focused ultrasound (HIFU) have been developed. RF is currently the most widely used modality of ablative therapy for HCC. Phase I and II clinical trials with HIFU have shown complete ablation and better long-term survival compared with PEI in randomised controlled trials. It employs thermal energy of vibration of ions in cells induced by radiofrequency wave to achieve protein coagulation and cell death. It has the merits of a minimally invasive therapy that can achieve effective local tumour ablation and preservation of normal liver parenchyma. Studies have demonstrated a complete ablation rate of above 90% for liver tumours less than 5 cm in diameter, and a treatment mortality rate of less than 1%. However, the safety of RFA depends on careful case selection and appropriate choice of approaches, which can be percutaneous, laparoscopic, thoracoscopic or open. While RFA is technically simpler compared with surgical resection of liver tumour, there is a learning curve that has to be overcome before RFA can be offered with satisfactory outcome. RFA is currently used mainly for unresectable HCC. It has offered a potentially curative treatment for patients with small HCC but poor liver function due to underlying cirrhosis, who otherwise did not have effective treatment in the past except for liver transplantation. There is some preliminary evidence that RFA may achieve survival results comparable to that of liver resection for small HCCs, although the evidence is not strong enough to recommend RFA as a replacement of resection. A high local recurrence rate is a problem of RFA that requires further research to resolve. Microwave and HIFU are two emerging modalities that may offer some advantages over RFA. It is foreseeable that the role of local ablative treatment of HCC will continue to expand in the near future.
Update on Obstetrics

Jointly organized by:
The Federation of Medical Societies of Hong Kong
香港醫學組織聯會

The Obstetrical and Gynaecological Society of Hong Kong
香港婦產科學會

Objective: This course is aimed for midwives, nurses, general practitioners or other allied health workers who are interested to learn about the recent advances in the field of obstetrics. There are many changes in the management of pregnant women right from the antenatal period, including invasive and non-invasive prenatal diagnostic techniques, management of the normal, abnormal and high risk pregnancies. Advances in the intrapartum and postpartum management will also be discussed. The concept and delivery of midwifery care have undergone tremendous changes in the recent decade and will be further explored.

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<td>梁哲賢專科護士</td>
<td>助產士在現代產科的角色</td>
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Date: April 3, 10, 24 & May 8, 15, 22, 2008
Time: 7:00 p.m. - 8:30 p.m.
Venue: Lecture Hall, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, HK
Course Fee: HK$750 (6 Sessions)
Language: Cantonese supplemented with English
Certificate: Awarded to participants with a minimum attendance of 70%
Enquiry: The Secretariat of the Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax: 2865 0345 Email: info@fmshk.org

CME/CPD accreditation applied; OGSHK CNE/PEM point pending
To download the application form, please visit our website: http://www.fmshk.org
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<th>Sunday</th>
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<td>Kidney Disease Awareness Day</td>
<td>When Should We Take an Infected Kidney Out?</td>
<td>FMSHK Officers’ Meeting</td>
<td>HKMA Council Meeting</td>
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<td>Friday Day</td>
<td>HKMA Structured CME Programme at Queen Elizabeth Hospital Year 07/08 (XII) - Clinical Oncology and Cardiothoracic Surgery</td>
<td>HKMA Newsletter Editorial Meeting</td>
<td>Wound Management in Disasters (Code No. SE-WMD-0108)</td>
<td>Hong Kong Neurosurgical Society Monthly Academic Meeting - Radiosurgery : Past, Present &amp; Future</td>
<td>HKMA Structured CME Programme with Hong Kong Sanatorium &amp; Hospital Year 2008 (III)</td>
<td>Advanced Trauma Life Support (ATLS) Provider Course</td>
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<td>FMSHK Officers’ Meeting</td>
<td>FMSHK Executive Committee Meeting</td>
<td>8 Lessons in Practical Psychiatry for General Practitioners: A Certificate Course</td>
<td>Interpretation of Arterial Blood Gases and Essential Electrolytes Imbalance</td>
<td>8 Lessons in Practical Psychiatry for General Practitioners: A Certificate Course</td>
<td>HKMA Structured CME Programme at Kwong Wah Hospital Year 07/08 (XII) - Rehabilitation &amp; Palliative Care</td>
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Date / Time | Function | Enquiry / Remarks
---|---|---
2 1:00 pm | Kidney Disease Awareness Day | Miss Gloria CHEUNG
| | | Tel: 2527 8285
| | Glaucoma Public Awareness Day | Dr. Dexter LEUNG
| | | Email: dexterleung@gmail.com
3 7:30 pm - 8:30 pm | When Should We Take an Infected Kidney Out? | Dr. CHAN Kwok Keung,
| | | Sammy/Ms Siddly MA
| | | Tel: 2958 6066 Fax: 2958 6076
| | | 1 CME Point
4 8:00 pm - 10:00 pm | HKM CME Board Meeting | Secretariat
| | | Tel: 2527 8988 Fax: 2865 0345
5 8:00 pm | HKMA Council Meeting | Ms. Christine WONG
| | | Tel: 2527 8825
6 8:00 pm | HKMA CME Board Meeting | Ms. Clara TSANG
| | | Tel: 2354 2440
| | | 2 CME Points
7 8:00 pm | HKMA Newsletter Editorial Meeting | Ms. Tammy TAM
| | | Tel: 2527 8941
| 7:30 pm - 8:30 pm | Wound Management in Disasters (Code No. SE-WMD-0108) | Secretariat
| | | Tel: 2527 9255 Fax: 2838 6280
| | | 1.5 CME Point
8 12:00 pm | Football Day | Ms. Dora HO
| | | Tel: 2527 8285
9 2:00 pm | HKMA Structured CME Programme at Queen Elizabeth Hospital Year 07/08 (XII) - Clinical Oncology and Cardiothoracic Surgery | Miss Viviane LAM
| | | Tel: 2527 8452
| | | (Registration Fee is required)
| | | 3 CME Points
10 8:00 pm | HKM CME Board Meeting | Ms. Clara TSANG
| | | Tel: 2354 2440
| 7:30 am | Hong Kong Neurosurgical Society Monthly Academic Meeting - Radiosurgery : Past, Present & Future | Dr. Y.C. PO
| | | Tel: 9527 8452 (Registration Fee is required)
| | | 1 CME Point
11 12:00 pm | Joint Professional Golf Tournament 2008 | Ms. Clara TSANG
| | | Tel: 2527 8285
| | | 1 CME Point
| 2:00 pm | HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2008 (II) | Miss Viviane LAM
| | | Tel: 2527 8452 (Registration Fee is required)
| | | 1 CME Point
12 (15,16) 2:00 pm | Advanced Trauma Life Support (ATLS) Provider Course | Program Manager
| | | Tel: (852) 2835 4886 / 2855 4886
| | | Fax: (852) 2819 3416
| | | Email: gmlsdc@hkuec.hku.hk
| 8:00 pm - 10:00 pm | FMSHK Executive Committee Meeting | Secretariat
| | | Tel: 2527 8988 Fax: 2865 0345
13 6:00 pm - 8:00 pm | Interpretation of Arterial Blood Gases and Essential Electrolytes Imbalance | Mr. Jacky LAM
| | | Tel: 9524 6160
| | | 4 CME Points
14 2:00 pm | 8 Lessons in Practical Psychiatry for General Practitioners: A Certificate Course | Miss Gloria CHEUNG
| | | Tel: 2527 8285
| | | 1 CME Point
15 8:00 pm | Kidney Disease Awareness Day | Miss Gloria CHEUNG
| | | Tel: 2527 8285
| | | 1 CME Point
16 8:00 pm | HKMA CME Board Meeting | Secretariat
| | | Tel: 2527 8988 Fax: 2865 0345
17 8:00 pm | HKMA CME Board Meeting | Ms. Clara TSANG
| | | Tel: 2354 2440
| | | 2 CME Points
18 8:00 pm | HKMA CME Board Meeting | Ms. Clara TSANG
| | | Tel: 2354 2440
| | | 2 CME Points
19 8:30 am - 9:30 am | When Should We Take an Infected Kidney Out? | Dr. CHAN Kwok Keung,
| | | Sammy/Ms Siddly MA
| | | Tel: 2958 6066 Fax: 2958 6076
| | | 1 CME Point
20 8:00 pm | HKMA CME Board Meeting | Ms. Clara TSANG
| | | Tel: 2354 2440
| | | 2 CME Points
21 8:00 pm | HKMA CME Board Meeting | Ms. Clara TSANG
| | | Tel: 2354 2440
| | | 2 CME Points
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23 8:00 pm | HKMA CME Board Meeting | Ms. Clara TSANG
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24 8:00 pm | HKMA CME Board Meeting | Ms. Clara TSANG
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25 8:00 pm | HKMA CME Board Meeting | Ms. Clara TSANG
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27 8:00 pm | HKMA CME Board Meeting | Ms. Clara TSANG
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28 8:00 pm | HKMA CME Board Meeting | Ms. Clara TSANG
| | | Tel: 2354 2440
| | | 2 CME Points
29 8:00 pm | HKMA CME Board Meeting | Ms. Clara TSANG
| | | Tel: 2354 2440
| | | 2 CME Points
30 8:00 pm | HKMA CME Board Meeting | Ms. Clara TSANG
| | | Tel: 2354 2440
| | | 2 CME Points
Meetings

2-4/5/2008 16th Annual Scientific Congress of Hong Kong College of Cardiology
Organised by: Hong Kong College of Cardiology Chairman: Dr. CHIANG Chung Seung # Sheraton Hong Kong Hotel & Towers, 20 Nathan Road, Tsimshatsui, Kowloon Enquiry: Ms. Dora HO Tel: 2527 8285 Fax: 2865 0943 Email: dorahkma@hkma.org Website: http://www.hkckh.com/scientificcongress.php

17-18/5/2008 9th Regional Osteoporosis Conference
Organised by: Osteoporosis Society of Hong Kong & Hong Kong College of Radiologists Speaker: International & Regional Experts # Hong Kong Convention & Exhibition Centre Enquiry: Ms. Renora YUNG Tel: 2871 8885 Fax: 2819 3416 Email: hksf@hkucc.hku.hk Website: http://www.hku.hk/surgery

24-25/5/2008 Annual Scientific Meeting “Family Physicians and Our Community”
Organised by: Hong Kong College of Family Physicians Chairman: Dr. Winnie W.Y. CHAN # HKAM Jockey Club Building Enquiry: Ms. Erica SO Tel: 2528 6618 Fax: 2866 0618

11-12/7/2008 Hong Kong Surgical Forum, Summer 2008
Organised by: Department of Surgery, Li Ka Shing Faculty of Medicine, University of Hong Kong Medical Centre; Queen Mary Hospital & Hong Kong Chapter of the American College of Surgeons # Underground Lecture Theatre, New Clinical Building, Queen Mary Hospital, Pokfulam, Hong Kong Enquiry: Forum Secretary Tel: 2855 4885 Fax: 2819 3416 Email: info@cardiorhythm.com Website: http://www.cardiorhythm.com

20-22/2/2009 CardioRhythm 2009
Organised by: Hong Kong College of Cardiology & Chinese Society of Pacing and Electrophysiology Co-Chairman: Prof. LAU Chu Pak Enquiry: Secretariat Tel: 2899 2035 Fax: 2899 2045 Email: info@cardiorhythm.com Website: http://www.cardiorhythm.com

Courses

2,9,16,23,30/5/2008 ISCD Bone Densitometry Course
Organised by: Osteoporosis Society of Hong Kong Chairman: Prof. Annie KUNG Speaker: International & Local Experts # Hong Kong Convention and Exhibition Centre, Wanchai, Hong Kong Enquiry: Ms. Renora YUNG Tel: 2871 8885 Fax: 2819 3416 Email: info@cardiorhythm.com Website: http://www.cardiorhythm.com

Upcoming Certificate Courses of the Federation of Medical Societies of Hong Kong

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<th>Course No</th>
<th>Course Name</th>
<th>Co-organiser</th>
<th>Target Participants</th>
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<tr>
<td>3 Apr - 22 May 08</td>
<td>C128</td>
<td>Update on Obstetrics</td>
<td>The Obstetrical and Gynaecological Society of Hong Kong</td>
<td>Midwives, Nurses and other Allied Health Workers</td>
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<tr>
<td>10 Jun - 8 Jul 2008</td>
<td>C129</td>
<td>Certificate Course on Drug Dispensing in Office Clinics</td>
<td>Medical and Health Care Professional</td>
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Answer to Clinical Quiz

Answer - Malrotation

The abdominal radiograph shows that the stomach and the proximal duodenum are distended with air. The bowels are otherwise devoid of bowel gas. Features are suggestive of duodenal obstruction.

Upper GI contrast study is thus proceeded to find out the possible causes of obstruction. It shows that the duodenojejunal junction is abnormally on the right side of the vertebral column and below the level of the duodenal bulb. Twisting or coackswirl appearance suggesting Ladd’s band is seen at the distal duodenum and proximal jejunum which are located on the right side of the abdomen. Findings are compatible with malrotation.

Malrotation associated with midgut volvulus is a surgical emergency in infants which can lead to bowel obstruction, ischaemia and necrosis. The baby boy had an urgent operation (Ladd’s procedure) and the radiological findings were confirmed.

Dr. Ka-kin Wong
MBBS, FRCR
Queen Mary Hospital
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References:
2. Takepron® package insert. Takeda Chemical Industries (Galaxar) Ltd. Hong Kong Branch

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Tel: (852) 2881 2218 Fax: (852) 2829 4216 http://www.takeda.com