Welcome to our June 2018 Newsletter!

It was my honour to take over as president from Professor Justin Wu and formed a new council. I would like to welcome our new Vice President Dr Jodis T.W. Lam, new Honorary Secretary Dr Chi-Ming Lam, new Honorary Treasurer Dr Wai-Cheung Lao and three new co-opted members Dr Kelvin K.C. Ng, Professor Siew C Ng and Dr Walter W.K. Seto. On behalf of the Society, I would like to thank everyone in the Council for their valuable contributions to the Society in the past two years especially Professor Wu for leading the council.

Our Society has never stopped making efforts in organizing activities to promote the advancement of gastroenterology. On 22 March 2018, the Annual General Meeting cum Scientific Meeting was held during which honorary fellowship was bestowed upon Professor Emad M El-Omar, Professor of Medicine, University of New South Wales, Australia cum Editor in Chief, GUT. While the 19th Joint Annual Scientific Meeting (JASM) was incorporated into Asian Pacific Digestive Week 2017, the 20th JASM will be held on 26 August 2018 at Cordis, Hong Kong Hotel at Mongkok.

I would like to thank Dr Wai-Fan Luk for organizing the Annual General Meeting cum Scientific Meeting on 22 March 2018, Professor Wai-Keung Leung for editing this Newsletter, Professor Emad M El-Omar and Dr Michael Hang-Hoi Wong for their scientific updates in this Newsletter and last but not least, all the sponsors who rendered support and contributions to the Society.

The next newsletter will be published in December 2018.

Dr. Annie O.O. Chan
President, The Hong Kong Society of Gastroenterology

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**Professor Emad M El-Omar**
Professor of Medicine
St George & Sutherland Clinical School
University of New South Wales
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Editor in Chief, GUT

**Dr. Nan Wu, Dr. Howard Yim**
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Australia
The gut microbiota are the microbial communities colonizing the gastrointestinal tract and the microbiome is the collective genomes of all the microbes and their metabolic output. The microbiome has a huge impact on the host and contributes to a multitude of essential functions including development and education of the immune system, fortification of the gut epithelium and protection against pathogens. In addition to their effect on immunity, the gut microbiota also produce metabolites which interact with and impact on host health and disease. Common metabolites are short chain fatty acids (SCFAs), vitamins, organic acids, bile salts and lipids.1

Two important concepts underpin our understanding of the role of the gut microbiome in human health. The first is that microbial diversity is beneficial to the host and imparts a healthy state, while loss of diversity is often identified with disease states. The second concept is that loss of balance between beneficial and harmful microbiota (dysbiosis) leads to a state of chronic inflammation, the pathophysiological basis of most human diseases. Understanding the causes and mechanisms of dysbiosis offers an opportunity to prevent, ameliorate and cure disease.

The list of human diseases that have been associated with loss of diversity and dysbiosis is ever expanding and includes almost all human systems. Suffice to say that in recent years some fascinating mechanistic work has started to appear in the literature lending credence and plausibility to these early associations. This is particularly true for major GI disease such as IBD and colorectal cancer (CRC).

In the case of IBD, the composition of gut microbiota in patients has been extensively studied over the last decade. Although methodologies differ, some generalisations are possible. There is ample evidence to suggest loss of diversity is a major feature of Crohn’s disease (CD) and ulcerative colitis (UC). This biodiversity, known as alpha-diversity or species richness in ecological terms, is a measure of the total number of species in a community.

In the largest IBD-related microbiome study to date, Gevers et al.2 analysed the treatment-naive microbiome in new-onset CD found a strong association between disease status and an overall decrease in species richness and altered taxa abundance.

Imbalance between pathogenic and protective microbial populations
Several bodies of work have identified a distinct disease-state microbial signature characterised by increased numbers of disease-potentiating microbes and reduced population of protective microbes.

• Increased proportion of:
  o Enterobacteriaceae, Gammaproteobacteria and Clostridium difficile
  o Fusobacterium species. These have been found to be at higher abundance in the colonic mucosa of patients with UC relative to control and in patients with UC who underwent pouch surgery.
  o E. coli pathovar. This adherent-invasive strain is at higher abundance in the Crohn’s-affected mucosa and granulomas. In vitro, they invade epithelial cells and can replicate within macrophages and induce granuloma formation.3

• Decreased proportion of:
  o Bacteroidales, Firmicutes, Clostridia, Ruminococcaceae, Bifidobacterium, Lactobacillus, Bacteroides, Roseburia, Odoribacter, Anaerostipes, and Faecalibacterium prausnitzii.4,5 These species protect the host from mucosal inflammation. Faecalibacterium prausnitzii has anti-inflammatory properties, and their depletion is associated with higher risk of recurrent CD after surgery. Short-chain fatty acids (SCFAs) are the energy source for colonic epithelial cells. They are produced through the fermentation of dietary fibre by certain bacteria such as the Ruminococcaceae.
  o Other nonbacterial members of the microbiota, namely the fungi, viruses, archaea, and phage, may have a significant role in gastrointestinal disease; however, the vast majority of recent studies of the microbiota are based on 16S rRNA sequencing, thus largely ignoring these groups of organisms. The relationship between these organisms and IBD will no doubt be explored in more detail in the coming years, because microbiome studies will increasingly be performed by unbiased shotgun sequencing.

In summary, many IBD susceptibility loci suggest an impaired response to microbes in disease, but the causality of this relationship is unclear. The pathogenesis of IBD may result from a dysregulation of the mucosal immune system driving a pathogenic immune response against the commensal gut microbiota.

Colorectal cancer (CRC) offers another paradigm of microbiome-related carcinogenesis but how does the microbiota impact CRC development? Five non-mutually exclusive hypotheses have been proposed to explain how the microbiota influences the initiation and progression of CRC. The alpha-bug hypothesis suggests that CRC is initiated by the activities of the alpha-bugs, the particular microbes with specific virulence factors.6 These bugs are suggested to persist at the affected tissue fit with the changed milieu. The mucosal microbiota is always enriched in the inflamed colon.7 While the abundance of Bacteroides and Prevotella spp and Fusobacterium nucleatum at the CRC tissues8. On the other hand, a recent study that followed up the evolution of luminal microbiota in a azoxymethane-induced colon cancer animal model demonstrated that Bacteroidetes and Porphyromonadaceae are enriched in the inflamed colon.9 While the abundance of Rikenellaceae and Ruminococcaceae increases with the CRC progression, the abundance of Prevotellaceae and Enterobacteriaceae decreases with the process.10 These data support the idea of driver-passenger shift throughout the CRC development.

The intestinal microbiota adaptation hypothesis suggests that the gut microbial ecosystem is in dynamic equilibrium that is affected by various factors including diet, infection, antibiotic exposure and immune senescence. Thus, the gut microbiota exists in an adaptation to the changing gut environment. If these
In the largest IBD-related microbiome study to date, Gevers et al. amply evidence to suggest loss of diversity is a major feature of the composition of gut microbiota in patients lending credence and plausibility to these early literature. The list of human diseases that have been associated with loss of diversity is often identified with disease states. The second opportunity to prevent, ameliorate and cure disease. The pathophysiological basis of most human diseases. Imbalance between pathogenic and protective microbes.

Common metabolites are short chain fatty acids (SCFAs), effect on immunity, the gut microbiota also produce metabolites education of the immune system, fortification of the gut microbiome has a huge impact on the host and contributes to a protective immune response against the commensal gut microbiota. The relationship between these organisms and IBD will no doubt be explored in more detail in the coming years, The relationship between these organisms and IBD will no doubt be explored in more detail in the coming years, The driver-passenger hypothesis offers another paradigm of microbiota. The driver-passenger hypothesis suggests that CRC is initiated by the activities of the alpha-bug. These bugs are suggested to persist at the affected tissue and promote carcinogenesis by altering the local microbiota. The driver passes on the cancer cell, followed by colonization with oral species including other nonbacterial members of the microbiota, namely the Bacteroidales, Firmicutes, Clostridia, Ruminococcaceae.

The biofilm effect hypothesis suggests that gut microbes form structures with aggregates of cells coated in an exopolymeric matrix that can adhere and fix to the certain location of the gut. These microbial biofilms are found more often in right sided tumor proximal to the hepatic flexure. They invade the mucus layers, promoting the epithelial cell proliferation. They also elevate the polyamine metabolites which have been suggested to promote colon carcinogenesis, microbial cell growth and biofilm formation. Interestingly, Fusobacterium nucleatum plays a role in the formation of biofilms in the oral cavity. As Fusobacterium nucleatum and other oral microbes are often enriched in CRC-associated tissues, it is possible that these oral microbes may play similar role in biofilm formation during CRC development.

The commensal-driven bystander effect hypothesis suggests that commensal microbes can lead to the release of diffusible mutagenic agents by the infected host cells which cause DNA damage in other non-infected cells. E. faecalis is an example that utilizes this strategy to drive colon cell transformation.

In summary, it is very clear that the microbiome field offers a unique insight into pathogenesis of many human diseases, including ones that we, as gastroenterologists, try to treat on a daily basis. We are very fortunate to be the custodians of this very exciting revolution in medicine and we owe it to the world to translate all our research into strategies for treating, curing and preventing GI and liver disease. The future of our specialty has never been brighter!

References
7. S. H. Hong et al., Gavage of Fecal Samples From Patients with Colorectal Cancer Promotes Intestinal Carcinogenesis in Germ-free and Conventional Mice. Gastroenterology, 2017; 153:1621-1633.
11. X. Wang, Y. Yang, M. M. Huycke, Commensal bacteria drive endogenous transformation and tumour stem cell marker expression through a bystander effect. Gut. 2015; 64, 459-469.
Is It Time To Change Our First Line Helicobacter Pylori Eradication Therapy? Clinical Trial: Levofloxacin-Containing Triple Therapy Versus Clarithromycin-Containing Triple Therapy In Hong Kong – A Single Centre, Double Blinded Study (Summary of Thesis 2016)

**Abstract**

**Background**
Studies worldwide have demonstrated the rising prevalence of clarithromycin resistant strains, resulting in decline of eradication rate for Helicobacter pylori infection. We proposed a 7-day levofloxacin-based triple therapy as an alternative in our locality. The primary aim of this study was to compare a 7-day levofloxacin-based triple therapy with the standard 7-day clarithromycin-based triple therapy for the eradication of H. pylori infection in patients naïve to treatment in Hong Kong. The trial was designed as a non-inferiority trial.

**Methods**
A prospective, single-centre, double-blinded, randomized controlled trial was conducted in United Christian Hospital in Hong Kong. 220 consecutive H. pylori positive patients were recruited and randomly assigned to receive either 1 week of LAP (levofloxacin 250mg BD, amoxicillin 1g BD, pantoprazole 40mg BD) or 1 week of CAP (clarithromycin 500mg BD, amoxicillin 1g BD, pantoprazole 40mg BD). Eradication of H. pylori was assessed at week 6 post treatment with 13C-urea breath test.

**Results**
Intention-to-treat analysis (ITT) showed that H. pylori eradication was achieved in 74.5% and 75.5% of candidates and per protocol analysis (PP), 82.0% and 80.6%, following 7-day triple therapy of LAP and CAP respectively. The eradication rates between the two therapy, either by ITT (p=0.973) or PP (p= 0.796) did not differ.

**Conclusions**
7-day clarithromycin-based triple therapy remained to be an effective first line H. pylori eradication therapy in Hong Kong. On the other hand, 7-day levofloxacin-based regimen has also demonstrated similar efficacy against H. pylori, and can be considered as first line H. pylori eradication therapy.

**Background**
*Helicobacter pylori* (H. pylori) causes a common chronic bacterial infection in Hong Kong. In 2010, the World Health Organization (WHO) reported that *H. pylori* was found in half of the world’s population. Despite its highly variable prevalence, a decreasing trend in the prevalence of *H. pylori* in many parts of the world was observed in recent years. Nevertheless, *H. pylori* is an important factor in the development of peptic ulcers, chronic gastritis, duodenitis, and gastric malignancies. Therefore, it is important to formulate a strategy for eradication of *H. pylori*.

The efficacy of different regimens, comprising of proton pump inhibitor and antibiotics, were studied in various areas worldwide. Antimicrobial drug resistance is the major cause of failure in *H. pylori* eradication and is also responsible for the decline in the eradication rate. Resistance rates vary remarkably in different geographic areas; therefore, the selection of therapeutic regimens needs adjustments on the basis of the local resistance pattern. The first-line treatment in Hong Kong involves proton pump inhibitor (PPI), clarithromycin, and amoxicillin. However, the long-term use of clarithromycin as monotherapy, mainly for respiratory tract infections, has led to high *H. pylori* clarithromycin-resistance rates.

A randomised controlled trial in 2009 demonstrated that the standard 7-day clarithromycin-based triple therapy was still the most effective empirical first-line eradication therapy with an eradication rate of 92.7% for *H. pylori* infection in Hong Kong. However, the prevalence of primary resistance of *H. pylori* to amoxicillin and clarithromycin remains low. Nevertheless, numerous global epidemiology studies demonstrated that the standard therapy’s eradication rate has decreased to 80% or below in Asia. Physicians are responsible in making up-to-date validation of the usefulness of the standard therapy, as well as in determining whether better substitutes are available.

In Italy, Nista et al. demonstrated that a 7-day levofloxacin-based triple therapy can achieve higher *H. pylori* eradication rates than those achieved by standard regimens. Another Italian study showed that a 10-day levofloxacin-based therapy is better than the standard quadruple regimen as a second-line option for *H. pylori* eradication. In China, none of the regimens tested in 2012 achieved 90% or greater therapeutic efficacy. However, compared with other regimens, the levofloxacin-based therapy demonstrated superior result. In 2010, a study in Taiwan demonstrated that clarithromycin-based triple therapy achieved a higher eradication rate than that obtained by levofloxacin-based triple therapy as first-line treatment.
Objectives
The primary objective of this study mainly compared the efficacy of a 7-day levofloxacin-based triple therapy with that of a standard 7-day clarithromycin-based triple therapy in patients suffering from H. pylori infection. This study also assessed whether the current standard first-line treatment for H. pylori infection remains valid. Furthermore, this study evaluated the susceptibility testing of patients who failed with the first-line treatment.

Patients and Methods
This prospective, double-blinded randomized trial was performed by the Division of Gastroenterology, Department of Medicine and Geriatrics, United Christian Hospital, Hong Kong. The study had been approved by the Hospital Authority Kowloon Central / Kowloon East Cluster Research Ethics Committee.

Patients suffering from H. pylori infection and willing to comply with our regimens were prospectively recruited. The patients were enrolled between August 2015 and April 2016 in an outpatient setting. The indications of their endoscopy were retrospectively collected. The patients were recruited consecutively during this period when their histology results demonstrated the presence of H. pylori. The histology results were screened, and the patients were asked to return to the clinic for eradication treatment.

Patients eligible to participate in the study were male or female adults (≥18 years) with histological diagnosis of H. pylori infection. The major exclusion criteria are the following: patients with previous treatment for H. pylori infection; patients who had recent use of antibiotics and/or proton pump inhibitors (6 weeks prior to study); patients with active gastrointestinal malignancy; patients with severe cardiac, respiratory, endocrine, hepatic, and hematological disorders; patients with severe neurological or psychiatric disorders; patients with allergies toward the study drug; alcoholics or recreational drug users; pregnant women or women during their lactation periods; and patients with simultaneous participation in another clinical trial.

Histological specimens were obtained via endoscopy. Our hospital’s protocol required our endoscopists to acquire two specimens for histology testing: one sample from the antrum and another from the body. H. pylori infection was defined to be positive when either or both of the samples demonstrated positive.

Patients were randomly allocated to receive one of the two treatment regimens by using a computerized binary system. One group was treated with a 7-day levofloxacin-based triple therapy (LAP), comprising 40 mg of pantoprazole twice daily, 1 g of amoxicillin twice daily, and 250 mg of levofloxacin twice daily for 7 consecutive days. The second group was treated with standard 7-day clarithromycin-based triple therapy (CAP), comprising 40 mg of pantoprazole twice daily, 1 g of amoxicillin twice daily, and 500 mg of clarithromycin twice daily for 7 consecutive days.

A sequence of randomized numbers was generated. An independent medical staff member assigned the subjects to the two schedules. All enrolled patients were interviewed at the beginning of the trial with detailed explanation of the treatment regimens, the possible adverse effects, and the importance of compliance and post-treatment with 13C-urea breath test. Each patient was required to sign a written consent form and demonstrate understanding of their rights in this clinical trial. Compliance was defined as the completion of the 7-day triple therapy of whichever arm, in a consecutive manner. Upon 13C-urea breath test at week 6 and follow-up clinic appointment at week 8, compliance was checked. Unused study medications were brought to a follow-up clinic appointment. Adverse events were questioned during the follow-up clinic appointment.

Statistical Analysis
This study was designed to show the non-inferiority efficacy of the levofloxacin-based regimen versus the standard clarithromycin-based regimen. The sample size was calculated with a non-inferiority margin, δ = 10%. The value of 10% was based on the current recommendation of the Food and Drug Administration for anti-infective trials, regardless of the specific type or severity of infection. This value indicated how much the efficacy of the active control (clarithromycin-based regimen) can exceed the efficacy of the new treatment (levofloxacin-based regimen), with the new treatment still considered non-inferior to the active control.

A sample size of 100 patients per treatment group was calculated to be sufficient. However, we decided to increase the population to 110 patients per treatment group to compensate for a potential 10% loss at follow-up treatment. This calculation was based on a non-inferiority margin (i.e., δ) of 10%, upper and lower confidence intervals (CIs) varying from −10% to +1%, a power of 0.80, and a significance level of 0.05 (one-sided a level of 0.05).

Both intention-to-treat (ITT) and per-protocol (PP) analyses were used to assess the eradication rates of H. pylori infection in the two groups. Odds ratios for achieving H. pylori eradication with 95% CI were calculated. The significance level was set at P < 0.05.

The nominal data, including gender, smoker versus non-smoker status, and alcohol consumption versus non-alcohol consumption; endoscopic diagnosis in the two treatment arm groups; adverse events; and symptom improvements at post treatment, were all compared by chi-squared test and Fisher’s exact test.
The difference in patients’ age in the two groups was examined by Student’s t-test. A two-sided P < 0.05 was considered statistically significant.

Eradication rates achieved with the two therapeutic regimens were compared by chi-squared test, and a one-sided (i.e., non-inferiority) P < 0.05 was considered statistically significant.

Statistical analysis was performed using SPSS version 22.0.

**Results**

**Patient characteristics**

A total of 220 patients with a diagnosis of *H. pylori* infection were enrolled in this study. The baseline demographics were similar in both LAP and CAP groups. The mean age was 56.6 ± 13.09 years in the LAP group and 57.2 ± 13.00 years in the CAP group. Up to 43.6% and 48.2% were male participants in the LAP and CAP groups, respectively. Endoscopic findings of gastritis, gastric ulcer, duodenal ulcer, esophagitis, and duodenitis, as well as normal findings were similarly distributed in both groups. Detailed baseline demographics and characteristics are summarized in **Table 1**.

**Table 1. Baseline demographics**

<table>
<thead>
<tr>
<th></th>
<th>LAP</th>
<th>CAP</th>
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<tbody>
<tr>
<td>Gender (M:F)</td>
<td>48 (43.6%)</td>
<td>53 (48.2%)</td>
</tr>
<tr>
<td>Age (mean +/- SD)</td>
<td>56.6 ± 13.09</td>
<td>57.2 ± 13.00</td>
</tr>
<tr>
<td>Endoscopic findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastritis</td>
<td>59 (53.6%)</td>
<td>61 (55.5%)</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>17 (15.5%)</td>
<td>15 (13.6%)</td>
</tr>
<tr>
<td>Duodenal ulcers</td>
<td>11 (10.0%)</td>
<td>15 (13.6%)</td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>5 (4.5%)</td>
<td>2 (1.8%)</td>
</tr>
<tr>
<td>Duodenitis</td>
<td>3 (2.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Normal findings</td>
<td>15 (13.6%)</td>
<td>17 (15.5%)</td>
</tr>
</tbody>
</table>

**Table 2. Treatment outcome**

<table>
<thead>
<tr>
<th></th>
<th>LAP, n (%)</th>
<th>CAP, n (%)</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Numbers of patients</td>
<td>110</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td>82 (74.5%)</td>
<td>83 (75.5%)</td>
<td>0.973</td>
</tr>
<tr>
<td>PP</td>
<td>82 (82.0%)</td>
<td>83 (80.6%)</td>
<td>0.796</td>
</tr>
</tbody>
</table>

ITT (intention to treat); PP (per protocol)

**Table 3. Adverse Events**

<table>
<thead>
<tr>
<th></th>
<th>LAP</th>
<th>CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Bloating</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Taste disturbances</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

**Total, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>LAP (7.8%)</th>
<th>CAP (17%)</th>
</tr>
</thead>
</table>
the tolerance of treatment in The current study clearly showed that the clarithromycin-based suggested that the resistance rate of clarithromycin was higher in the Maastricht IV/Florence Consensus Report because it is very susceptibility of all commonly used antibiotics, including 13C-urea breath test and follow-up clinic. any inquiries concerning the treatment regimen and its associated cannot determine the resistance rate of clarithromycin in the H. pylori which can be applied to other groups of antibiotics, including Determination of antibiotics of distant use is difficult within the Thus, patients who underwent endoscopy for their gastrointestinal to patients is proposed for future studies of similar nature. Hence, further delay was other infections, mainly respiratory tract infections. The stable clarithromycin-based regimen indirectly demonstrated the efficacy with the manufacturer’s instructions. Self-calibration was not. This finding was similar to the meta-analysis result presented by Ye et al. in 2013, with a cure rate of 77.2%. However, in different parts of Asia, the eradication rates demonstrated a large discrepancy. For example, Wang et al. conducted a single-centered randomization control trial of a similar size group in Shanghai, China, in 2015; in their study, theITT value for clarithromycin-based regimen was only 55.94%, and the PP value was 63.49%. Several studies in South Asia also demonstrated the ineffectiveness of this triple therapy as first-line treatment. The discrepancy is multifactorial. The factors include compliance, high gastric acidity, high bacterial load, different Helicobacter strains, and H. pylori resistance to clarithromycin, which is considered to be the most important and primary factor.

The primary clarithromycin-resistance rates in treatment-naive patients in China were reported to be 32% and 21.5% by De Francesco et al. and Su et al., respectively. In Japan, the corresponding rate was reported to be 29%; in India, the resistance rates was reported by Thyagarajan et al. to be 45% in 2003. Similar prevalence was found in West Asia. In Iran and Turkey, the primary H. pylori resistance to clarithromycin was 14.3% and 21%, correspondingly. European countries also demonstrated a steady increase in clarithromycin resistance, with Italy and Germany presenting values as high as 53% and 67.1%, respectively.

However, a contrasting example is in Taiwan, where macrolide consumption was restricted by the national policy since 2001. The prevalence of clarithromycin resistance was reported to be 7.9% by Jyh-Ming et al. Other Southeast Asian countries, where clarithromycin resistance rates are low, include Thailand with 3.7% and Singapore with 7.9%. Moreover, in Bhutan and Malaysia, no clarithromycin resistance has been reported. These countries have shown cure rates of >90% with clarithromycin-based regimen as their first-line eradication therapy.

The European Medicines Agency published three categories of bacterial species in accordance with their susceptibility to any given antibiotics in 2004. They are usually susceptible (0% to 10% resistant), inconstantly susceptible (10% to 50% resistant), and usually resistant (>50% resistant). Helicobacter pylori fall into the second category in Hong Kong and also for the rest of Asia. Evaluation of the efficacy of our first-line therapy for H. pylori eradication in Hong Kong and consideration of a substitute antibiotic regimen are important if our first-line treatment is not effective. Levofoxacin-based regimen was studied in this case.

### Table 4. Susceptibility profiles

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Amoxicillin</th>
<th>Clarithromycin</th>
<th>Levofloxacin</th>
<th>Metronidazole</th>
<th>Tetracycline</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP-1</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>CAP-2</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>CAP-3</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>CAP-4</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>CAP-5</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>CAP-6</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>CAP-7</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>CAP-8</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>LAP-1</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>LAP-2</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
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<tr>
<td>LAP-3</td>
<td>S</td>
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<td>R</td>
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<tr>
<td>LAP-4</td>
<td>S</td>
<td>S</td>
<td>R</td>
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<td>LAP-5</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
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S = sensitive R = resistant

### Table 5. Subgroup analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Odds ratio (p-value)</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Age (student t-test)</td>
<td>1.034 (0.022) *</td>
<td>1.005-1.063</td>
</tr>
<tr>
<td>Gender (chi square test)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.835 (0.638)</td>
<td>0.395-1.768</td>
</tr>
<tr>
<td>Ulcer status (chi square test)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-ulcer</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ulcer</td>
<td>1.881 (0.185)</td>
<td>0.739-4.793</td>
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*Statistically significant

### Susceptibility profiles

Forty participants tested to remain positive with H. pylori upon 13C-urea breath test after the first-line eradication therapy. A total of 34 participants agreed for repeat endoscopy and biopsy. H. pylori’s DNA were detected by PCR in all the 34 candidates’ samples, but only 13 samples demonstrated positive growth of H. pylori by culture. Eight samples belonged to the clarithromycin-based regimen group and demonstrated H. pylori resistance to clarithromycin. Four participants of this group showed resistance to both clarithromycin and levofloxacin. Five of the 13 participants received levofloxacin-based regimen, and all of them showed H. pylori resistance to levofloxacin, whereas three participants also demonstrated dual resistance to clarithromycin and levofloxacin. Table 4 presents the successfully cultured H. pylori from 13 candidates after failed eradication of the first-line treatment, as well as the susceptibility profiles toward the five commonly used antibiotics.

### Subgroup analysis

The three main subgroups were age, gender, and endoscopic findings of ulcer versus non-ulcer. Student t-test and chi-squared test were conducted accordingly. Age was the only subgroup which demonstrated a statistical significance with an odds ratio of 1.034 (p=0.022, CI 1.005-1.063). Table 5

### Discussion

According to the Asia-Pacific H. pylori Consensus Conference in 2009, the first-line treatment for H. pylori eradication should consist of clarithromycin-based triple therapy or bismuth quadruple therapy. The current guidelines from the American College of Gastroenterology (ACG) and National Institute for Health and Care Excellence (NICE) also recommended a triple regimen consisting of a proton pump inhibitor, clarithromycin, and amoxicillin (or metronidazole). The Maastricht IV report published in 2012 stratified the first-line treatment on the basis of the area’s clarithromycin-resistance rates as follows: clarithromycin-based regimen should be given as first-line treatment in areas where resistance remained to be less than 15% to 20%, and an alternative bismuth quadruple therapy should be given otherwise.

The ITT value of 75.5% and PP value of 80.6% achieved by the standard clarithromycin-based regimen were presented in this study. This finding was similar to the meta-analysis result presented by Ye et al. in 2013, with a cure rate of 77.2%. However, in different parts of Asia, the eradication rates demonstrated a large discrepancy. For example, Wang et al. conducted a single-centered randomization control trial of a similar size group in Shanghai, China, in 2015; in their study, the ITT value for clarithromycin-based regimen was only 55.94%, and the PP value was 63.49%. Several studies in South Asia also demonstrated the ineffectiveness of this triple therapy as first-line treatment. The discrepancy is multifactorial. The factors include compliance, high gastric acidity, high bacterial load, different Helicobacter strains, and H. pylori resistance to clarithromycin, which is considered to be the most important and primary factor.

The primary clarithromycin-resistance rates in treatment-naive patients in China were reported to be 32% and 21.5% by De Francesco et al. and Su et al., respectively. In Japan, the corresponding rate was reported to be 29%; in India, the resistance rates was reported by Thyagarajan et al. to be 45% in 2003. Similar prevalence was found in West Asia. In Iran and Turkey, the primary H. pylori resistance to clarithromycin was 14.3% and 21%, correspondingly. European countries also demonstrated a steady increase in clarithromycin resistance, with Italy and Germany presenting values as high as 53% and 67.1%, respectively.

However, a contrasting example is in Taiwan, where macrolide consumption was restricted by the national policy since 2001. The prevalence of clarithromycin resistance was reported to be 7.9% by Jyh-Ming et al. Other Southeast Asian countries, where clarithromycin resistance rates are low, include Thailand with 3.7% and Singapore with 7.9%. Moreover, in Bhutan and Malaysia, no clarithromycin resistance has been reported. These countries have shown cure rates of >90% with clarithromycin-based regimen as their first-line eradication therapy.

The European Medicines Agency published three categories of bacterial species in accordance with their susceptibility to any given antibiotics in 2004. They are usually susceptible (0% to 10% resistant), inconstantly susceptible (10% to 50% resistant), and usually resistant (>50% resistant). Helicobacter pylori fall into the second category in Hong Kong and also for the rest of Asia. Evaluation of the efficacy of our first-line therapy for H. pylori eradication in Hong Kong and consideration of a substitute antibiotic regimen are important if our first-line treatment is not effective. Levofoxacin-based regimen was studied in this case.
Fluoroquinolones, specifically levofloxacin, were demonstrated to be active against *H. pylori* in vitro, and many clinical studies have confirmed the efficacy of levofloxacin-based regimen as second-line and rescue treatments. As early as 2000, many researchers have published studies examining the treatment of *H. pylori* with levofloxacin-based regimen. In 2003, Nista et al. reported an eradication rate of >90% with levofloxacin-based triple therapy after failing the first-line therapy. Zullo et al. also showed an eradication rate of 83% as rescue therapy. Both studies were conducted in Italy, where clarithromycin resistance was known to be high and levofloxacin resistance was known to be low. In addition, they did not perform susceptibility testing to assess the resistance rate of clarithromycin and metronidazole. As a result, the actual influence of levofloxacin in overcoming the resistance of clarithromycin and metronidazole was unknown. Liou et al. conducted a randomized comparative trial with crossover design, considering levofloxacin-based regimen as both first- and second-line treatments; the group reported 74.2% and 76.9% eradication rates in the ITT and PP analyses, respectively, as compared with the standard clarithromycin-based regimen. The results were comparable but did not demonstrate any statistical significance. This result can be explained by the increase of fluoroquinolone-resistance rates in the past years in almost all bacterial species, including *H. pylori*, as reported by many global surveillance studies.

De Francesco et al. reported in a 2010 systemic review that the primary levofloxacin-resistance rate was higher in Europe than in Asia. Furthermore, among all Asian countries, Japan demonstrated a resistance rate of 14.9%, which is significantly higher than the resistance rate of 2.6% in Hong Kong. In Europe, the *H. pylori* resistance rate for levofloxacin was 14.1%. An even higher resistance rate was observed in Western or Central and Southern Europe (>20%) than in Northern European countries (<10%). Over the past 5 years, a significant increase of levofloxacin resistance was observed. The increasing trend in resistance rates was noted especially in Asia. The prevalence of levofloxacin resistance in Asia in 2015 increased to 25.28%. However, the discrepancy among countries remained to be highly variable with 20.6% in China, 57% in Japan, 24.55% in South Korea, 5.3% in Iran, and 2.6% in Malaysia. Taiwan’s primary levofloxacin resistance rose from 4.9% (2000 to 2007) to 13.4% (2011 to 2012). Other European countries have reported similar incidence. Extensive use and misuse of quinolones for other infections, including urinary tract and respiratory tract infections, led to the emergence and spread of resistant strains in Hong Kong and other countries.

The present study showed that 7-day levofloxacin-based regimen is not inferior to the standard 7-day clarithromycin-based regimen. This study was designed to compare the two regimens of the same duration. However, the efficacy of levofloxacin-based regimen can be limited by the shorter duration therapy. As a result, the efficacy of levofloxacin-based regimen was yet to be optimized.

Many authors have reported that the duration of therapy was more important than the dosage of levofloxacin in *H. pylori* eradication regimen. Di Caro et al. stated that the duration of treatment was a crucial factor, next to resistance, in influencing successful eradication. In Taiwan, Cheng et al. did not demonstrate a statistically significant difference in *H. pylori* eradication between the 500 and 1000 mg levofloxacin daily doses with the same duration. A systematic review also reported that a higher *H. pylori* eradication rate was achieved with a 10-day regimen than with a 7-day regimen (80% versus 68%). Furthermore, another Taiwan group showed a more substantial effect when levofloxacin-based regimen was extended to a 14-day regimen, achieving >90% eradication of *H. pylori*. This finding was supported by Mielikke et al. and Chuah et al., who reported that extending the length of quinolone-based triple therapies to 14 days can achieve eradication success of up to 95% with moxifloxacin and 93.6% with levofloxacin, respectively.

A Chinese group led by Liao et al. suggested that treatment success was slightly improved with the addition of bismuth despite high local levels of fluoroquinolone resistance. The eradication rate of *H. pylori* by levofloxacin-based regimen appeared to be equivalent, if not higher, when it was given once daily as opposed to multiple dosing. This finding can be explained by the pharmacokinetics of levofloxacin being a concentration-dependent antibiotic and not a time-dependent antibiotic. The therapeutic effect of levofloxacin is mostly correlated with the ratio of the area under the concentration-time curve to MIC, which predicted the clinical and microbiological outcomes.

In the present study, we did not test *H. pylori*'s susceptibility profiles in all patients during their pretreatment phase. Strains of *H. pylori* that were resistant to at least two antibiotics were defined as multi-drug resistance (MDR). *H. pylori* isolates. In the post-treatment susceptibility profiling, 7 out of 13 (54%) were MDR strains of *H. pylori*. However, they all share one common factor, which is sensitivity to amoxicillin (100%). Interestingly, among these 13 strains, tetracycline proved to be superior among the rest, wherein only one (0.07%) of the isolates demonstrated resistance.

The emergence of MDR strains of *H. pylori* is a global health concern. De Francesco et al. reported in a systematic review in 2006 that multiple resistant strains were detected in 8% of Asian patients, 15% of American patients, and 8.9% of European patients. Recently, a multi-centered cross-sectional study conducted in Spain demonstrated a high primary resistance of *H. pylori* to clarithromycin and levofloxacin. A study of a Japanese group showed that the incidence of quinolone-resistant strains was higher in patients with previous history of eradication failure (48%) than in those who were naive to treatment (34%). The incidence of quinolone resistance in clarithromycin-resistant strains (51.8%) was also significantly higher than that in clarithromycin-sensitive strains (22.1%).

The present study demonstrated that age (OR 1.034, p = 0.022) was an independent predictor of *H. pylori* eradication failure to both clarithromycin- and levofloxacin-based triple therapies. Similar results were found in a recently published study in China with similar population group. The resistance rate of clarithromycin was 16.67% in patients aged below 20 years old, whereas 23.02% in patients aged 71 years to 80 years old. The highest resistance rate to levofloxacin was also observed in patients aged 71 years to 80 years old (29.2%). This finding was presumably related to the increased prior antibiotic exposure, especially for levofloxacin, because the elderly group presented a very high incidence of urinary tract infection, warranting its use. Moreover, levofloxacin is rarely used in young adults. Some data
suggested that the resistance rate of clarithromycin was higher in children than in adults. However, the association of H. pylori resistance to fluoroquinolones with older age and in isolates of high-level resistance to clarithromycin was proven to be accurate.

Gender did not predict antibiotic resistance in our study. The results among other studies were variable. In 2012, Boyanova et al. demonstrated a female predilection for resistance in clarithromycin, which was hypothesized to be related to the high prevalence of gynecological infections. However, other countries showed a male predilection.

The current study clearly showed that the clarithromycin-based treatment group presented substantially more adverse events than the levofloxacin-based treatment group. Despite neither treatment group exerted any major adverse events affecting patients’ compliance; presumably, levofloxacin, which was better tolerated and, on a large scale, would positively influence the overall compliance rate and consequently the eradication rate when compared to clarithromycin. The meta-analysis based on the tolerance of treatment in H. pylori also stated that the 7-day levofloxacin-based triple treatment was significantly better than the 7-day standard triple treatment9.

Strength of the study
This study is a well-designed research conducted in a clinical practice setting, thus representing the real-world situation (i.e., the effectiveness of treatment regimens in typical and daily practice).

Participating patients, excluding the drop-outs, were 100% compliant with the protocol. High compliance was ensured by providing verbal and written instructions to all the patients. Direct contact to the research team was also given to all the patients for any inquiries concerning the treatment regimen and its associated adverse effects. Patient compliance was assessed during both 13C-urea breath test and follow-up clinic.

Limitations
The major limitation of this study was the lack of H. pylori susceptibility profiles in all the patients during their pretreatment phase, particularly of the two antibiotics of interest: clarithromycin and levofloxacin. Furthermore, a thorough study to test the susceptibility of all commonly used antibiotics, including amoxicillin, tetracycline, and metronidazole, was absent. Nevertheless, hospitals do not routinely perform H. pylori susceptibility testing unless the second-line treatment has failed. The process of testing all positive H. pylori culture is discouraged by the Maastricht IV/Florence Consensus Report because it is very expensive and difficult to perform.

Post-treatment susceptibility profiles were disappointing. Among the 40 participants tested to remain H. pylori positive upon 13C-urea breath test, only 34 participants agreed for repeat endoscopy and biopsy to aim for targeted treatment. Although H. pylori’s DNAs were detected by PCR in all the samples, we were only able to demonstrate the susceptibility profiles of 13 samples.

It is stated that the culture from biopsy specimens demonstrated the potential of leading to high sensitivity (>90%) under optimal conditions4, 5, but the literature reported sensitivity values of the culture varying from 50% to 70% in experienced laboratories4. Our sensitivity, 13 cultured positive samples (38.2%), seemed to be below the average of published values, rendering 61.8% of false-negative results. Nonetheless, the results did not only reflect the fragility of the bacterium but the inevitable suboptimal accuracy of this method. Furthermore, as discussed with the microbiology department, the main reason for the disappointing culturing results was the handling process. The biopsy specimens should not be exposed to air and should be placed either in a saline solution for short-term transport (maximum of 4 hours) or in a transport medium. However, some of the samples were delayed during transport, resulting in low sensitivity. In addition, the laboratory does not perform susceptibility testing for H. pylori. Hence, further delay was expected when the samples were sent to the microbiology laboratory in the Chinese University of Hong Kong.

The 13C-urea breath test was performed in our centre in accordance with the manufacturer’s instructions. Self-calibration was not developed, and the company’s recommendations were followed. The results demonstrated no false-positive results because patients who demonstrated positivity were subsequently enrolled for endoscopy (excluding those who were reluctant for a repeat endoscopy) and repeat biopsies confirmed the positive findings of the 13C-urea breath test. Among the possible limitations are the false negative results. Nevertheless, the guidelines were followed to reduce the false negative results. For instance, we ensured that patients underwent fasting overnight and that they did not take proton pump inhibitors or antibiotics 1 week before the 13C-urea breath test.

The adverse effect profiles of either arm were less than expected, especially with the clarithromycin-based regimen. This finding can be ascribed to the delayed follow-up appointments; hence, patients were unable to recall their experienced adverse effects. Provision of a list of adverse events with common adverse effects to patients is proposed for future studies of similar nature.

The present study was not designed to be a population study. Thus, patients who underwent endoscopy for their gastrointestinal complaints were sequentially enrolled, thereby limiting the generalizability of our results. Moreover, our results were only collected from one institution, the United Christian Hospital.

As previously discussed, prior antibiotics exposure could be an influence towards the overall resistance rate and hence, the H. pylori eradication. In this study, we did not evaluate any distant use of antibiotics of interest, but only excluding patients who have taken antibiotics up to 6 weeks prior to recruitment. Determination of antibiotics of distant use is difficult within the healthcare system of Hong Kong. Carothers et al. reported that the percentage of levofloxacin-resistant isolates increased with an increasing number of previous courses of levofloxacin received, which can be applied to other groups of antibiotics, including clarithromycin.

Another limitation was the lack of a placebo group in this study. However, this limitation was not a major concern because this study aimed to compare the levofloxacin-based triple therapy with the clarithromycin-based triple therapy and not to evaluate whether either treatment is effective. Moreover, it would be unethical to issue a placebo, knowing the primary endpoint was to eradicate H. pylori infection.

In summary, several important clinical points can be drawn from this study. Infections by H. pylori are inconsistently susceptible in our region, as determined by the European Medicines Agency. Therefore, deciding on an empirical eradication regimen is difficult. The empirical treatment for H. pylori eradication should be based on the clarithromycin-resistance rate in accordance with the Maastricht IV/Florence Consensus Report. The present study cannot determine the resistance rate of clarithromycin in the
locality. However, the high eradication rate of the standard clarithromycin-based regimen indirectly demonstrated the efficacy of a first-line treatment. The frequency of resistance to macrolides seemed to be parallel with the use of this therapeutic class to treat other infections, mainly respiratory tract infections. The stable eradication rate can be attributed to the reduced consumption of macrolides to treat other infections in Hong Kong.

The levofloxacin-based regimen demonstrated efficacy similar to that of our standard first-line eradication therapy. Thus, understanding the steady increase of levofloxacin-resistance rate and the emergence of MDR strains to keep clarithromycin as our first-line treatment is encouraged and would be consistent with the current guidelines. Additionally, this study highlighted the importance of the appropriate use of levofloxacin to limit the development of further antimicrobial resistance.

The provision of post-treatment tests to confirm the successful eradication of H. pylori is important because the overall failure rate was still high. In view of the major challenge of multi-drug resistant H. pylori strains, for patients who failed in the first course of therapy, the antimicrobial susceptibility testing can be useful for clinicians in guiding the choice of antibiotic agents in the second-line therapy regimen.

Conclusions
The 7-day clarithromycin-based regimen remained to be an effective first-line therapy for H. pylori eradication in Hong Kong. Similarly, the 7-day levofloxacin-based regimen demonstrated efficacy against H. pylori and can be considered as first-line therapy for H. pylori eradication.

References
the tolerance of treatment in children than in adults. However, the association suggested that the resistance rate of clarithromycin was higher in suboptimal accuracy of this method. Furthermore, as discussed upon 13C-urea breath test, only 34 participants agreed for repeat among the 40 participants tested to remain eradication should be based on effectiveness of treatment regimens in typical and daily practice). The major limitation of this study was the lack of adverse effects. Patient compliance was assessed during both practice setting, thus representing the real-world situation (i.e., the unethical to issue a placebo, knowing the primary endpoint was to whether either treatment is effective. Moreover, it would be as previously discussed, prior antibiotics exposure could be collected from one institution, the United Christian Hospital. Biopsy specimens should not be exposed to air and should be expected when the samples were sent to the microbiology 13C-urea breath test. Among the possible limitations are the of therapy, the antimicrobial susceptibility testing can be useful for is important because the overall failure rate was still high. In view of the major challenge of multi-drug macrolides to treat other infections in Hong Kong9. eradication rate can be attributed to the reduced consumption of infection in patients naïve to treatment in Hong 7.9%3 by Jyh-Ming et al. Other Southeast Asian countries, where corresponding rate was reported to be 29%; in India, the corresponding rate was reported to be 52%; and in China, the corresponding rate was reported to be 27%. Moreover, in Bhutan and Singapore with 2.9% and 7.9% respectively. Asia-Pacific countries have shown cure rates of >90% with 3.7% and 21%, correspondingly. European countries also corresponding rate was reported to be 29%; in India, the cure rate has been shown to be 90% with clarithromycin-based therapy. NICE also recommended a triple Consist of clarithromycin-based triple therapy or bismuth according to the Asia-Pacific eradication rate than that obtained by levofloxacin-based therapeutic efficacy. However, compared with other regimens, levofloxacin-based triple therapy can achieve higher cure rate. The present study showed that levofloxacin-based therapy significantly higher success rate than clarithromycin-based therapy. The rates of cure in the levofloxacin and clarithromycin groups were 64.3% and 46.4% respectively.*...
20th JOINT ANNUAL SCIENTIFIC MEETING 2018
Sunday, 26 August 2018

Date: Sunday, 26 August 2018
Venue: The Ballroom, Level 7
Cordis, Hong Kong
555 Shanghai Street, Mongkok
Kowloon, Hong Kong

Organizing Chairperson: Prof Justin Wu
Scientific Chairpersons: Dr Wan-Chee Sze, Dr Wai-Man Yip
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St George & Sutherland Clinical School
University of New South Wales
Australia
Editor in Chief, GUT

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Dr Wing-Yan MAK
Department of Medicine and Therapeutics
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