

WJG 20<sup>th</sup> Anniversary Special Issues (6): *Helicobacter pylori***Second and third line treatment options for  
*Helicobacter pylori* eradication**

Mingjun Song, Tiing Leong Ang

Mingjun Song, Tiing Leong Ang, Department of Gastroenterology, Changi General Hospital, Singapore 529889, Singapore  
Author contributions: Song M and Ang TL contributed equally to the manuscript.

Correspondence to: Tiing Leong Ang, MBBS, MRCP (UK), FRCP Edin, Associate Professor, Department of Gastroenterology, Changi General Hospital, 2 Simei Street 3, Singapore 529889, Singapore. [tiing\\_leong\\_ang@cgh.com.sg](mailto:tiing_leong_ang@cgh.com.sg)

Telephone: +65-6-8503558 Fax: +65-6-7816202

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**Abstract**

*Helicobacter pylori* is a highly successful bacterium with a high global prevalence and the infection carries significant disease burden. It is also becoming increasingly difficult to eradicate and the main reason for this is growing primary antibiotic resistance rates in a world where antibiotics are frequently prescribed and readily available. Despite knowing much more about the bacterium since its discovery, such as its genomic makeup and pathogenesis, we have seen declining treatment success. Therefore, clinicians today must be prepared to face one, two or even multiple treatment failures, and should be equipped with sufficient knowledge to decide on the appropriate salvage therapy when this happens. This article discusses the factors contributing to treatment failure and reviews the second and third-line treatment strategies that have been investigated. Established empiric second line treatment options include both bismuth based quadruple therapy and levofloxacin based triple therapy. Antibiotic testing is recommended prior to initiating third line treatment. In the event that antibiotic susceptibility testing is unavailable, third line treatment options include rifabutin, rifaximin and sitafloxacin based therapies.

reserved.

**Key words:** *Helicobacter pylori*; Treatment failure; Salvage therapy; Drug resistance; Microbial; Bismuth; Ofloxacin; Moxifloxacin; Metronidazole; Rifabutin; Rifaximin; Sitafloxacin

**Core tip:** The reasons for treatment failure in *Helicobacter pylori* eradication need not always be due to antibiotic resistance; compliance to therapy and duration should always be evaluated. Choice of therapy need not strictly adhere to guidelines; clinicians should first explore the antibiotic resistance prevalence in their treatment population if possible. Third line therapy generally shows better eradication if it was based on antibiotic susceptibility tests, but this can be time-consuming and more costly. Empirical third-line therapies have yet to show satisfactory eradication rates although most studies generally have smaller study populations.

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**INTRODUCTION**

Since the discovery of *Helicobacter pylori* (*H. pylori*) by Marshall and Warren in 1982, an immense amount of research has gone into this bacterium. *H. pylori* is known to be the “most successful human pathogen” infecting an estimated 50% of the global population; its prevalence is about 70% in developing nations and about 20%-30% in industrialized nations. The treatment of *H. pylori* infection is very important due to its high disease burden that comes in the form of dyspepsia, gastroduodenal ulcer-

**Table 1 Summary of consensus reports on *Helicobacter pylori* therapy**

Region	Consensus title	Year	1 <sup>st</sup> line treatment recommendations	Salvage therapy recommendations	Ref.
South America	3 <sup>rd</sup> Brazilian consensus	2013	PPI + amoxicillin 1 g and clarithromycin 500 mg twice daily for 7 d  (Replace amoxicillin with furazolidone 200 mg twice daily for penicillin allergy)	PPI + levofloxacin 500 mg once daily + amoxicillin 1 g twice daily for 10 d or PPI + levofloxacin 500 mg once daily + furazolidone 400 mg once daily for 7-10 d or bismuth-based quadruple therapy for 10-14 d	[7]
24 countries: United Kingdom, United States, Spain, Italian, Germany, France, Ireland etc.	Management of <i>Helicobacter pylori</i> infection-the maastricht IV/florence consensus report	2012	If clarithromycin resistance rate < 20%: PPI + amoxicillin + clarithromycin or bismuth-based quadruple therapy (Replace amoxicillin with metronidazole for penicillin allergy) If clarithromycin resistance rate > 20%: Bismuth-based quadruple therapy or Non-bismuth quadruple therapy (sequential/concomitant therapy)	2 <sup>nd</sup> line rescue: if clarithromycin resistance rate < 20%: bismuth-based quadruple therapy or PPI + levofloxacin + amoxicillin if clarithromycin resistance rate > 20%: PPI + levofloxacin + amoxicillin 3 <sup>rd</sup> line rescue: antibiotic susceptibility test first	[6]
Global	<i>Helicobacter pylori</i> in developing countries  World Gastroenterology Organization Global Guideline	2011	PPI + amoxicillin + clarithromycin (replace amoxicillin with metronidazole for penicillin allergy) or bismuth-based quadruple therapy	Bismuth-based quadruple therapy or PPI + levofloxacin + amoxicillin	[8]
Asia Pacific	Second Asia-Pacific Consensus Guidelines for <i>Helicobacter pylori</i> infection	2009	PPI + amoxicillin + clarithromycin for 7 d or bismuth-based quadruple therapy	PPI-amoxicillin-metronidazole_ or bismuth-based quadruple therapy or levofloxacin-based triple therapy or rifabutin-based triple therapy	[1]
Japan	Guidelines for the Management of <i>Helicobacter pylori</i> Infection in Japan: 2009 Revised Edition	2009	PPI + amoxicillin + clarithromycin for 7 d	2 <sup>nd</sup> line rescue: PPI + amoxicillin + metronidazole for 5-10 d  3 <sup>rd</sup> line rescue: PPI + amoxicillin + levofloxacin	[9]
Latin America	Latin-American Consensus Conference on <i>Helicobacter pylori</i> infection	2000	Omeprazole 20 mg, or lansoprazole 30 mg, or pantoprazole 40 mg, or rabeprazole 20 mg + clarithromycin 500 mg + amoxicillin 1000 mg twice a day for 7-14 d (preferably 10 d)	No specific recommendations	[10]

PPI: Proton pump inhibitor.

ative diseases, gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric malignancies. Disease pathogenesis is due to a complex interaction between host factors, bacterial virulence factors, and the resulting pathological cellular responses such as inflammation, increased cell proliferation, apoptosis and morphological change<sup>[1,2]</sup>.

The 1997 Asia-Pacific Consensus had established that acceptable eradication rates for the treatment of *H. pylori* infection are 90% or greater on a per-protocol (PP) analysis and 80% or greater on an intent-to-treat (ITT) analysis<sup>[3]</sup>. However, the widely used standard clarithromycin-based triple therapy regime first proposed in 1997 is no longer achieving satisfactory eradication rates in many countries<sup>[4,5]</sup>. The updated Asia-Pacific Consensus published in 2009 acknowledged that there was an increasing

rate of resistance to clarithromycin and metronidazole in parts of Asia and that this had led to lower efficacy of clarithromycin-based triple therapy. Nonetheless it stated that there was still a role for triple therapy as first line therapy for *H. pylori* infection<sup>[1]</sup>. The Maastricht IV consensus recommended that if the treatment population was known to have a clarithromycin resistance rate above 20%, clarithromycin-containing triple therapy should be avoided. Instead, bismuth-containing quadruple therapy (BQT) or non-bismuth quadruple therapy (either sequential or concomitant) could be used as first line empirical treatment. Across the world, consensus meetings had been held to recommend and update guidelines for *H. pylori* treatment in the best evidence-based manner for the region of interest. Overall the recommendations were similar<sup>[1,6-10]</sup> (Table 1).

Nonetheless, studies have shown that the failure rate of first line treatment regimens can be more than 20%<sup>[3-6,11]</sup>. Therefore, it is important that clinicians are vigilant about treatment failures and have a “rescue” plan ready. It must also be recognized that *H. pylori* reinfection, rather than failed therapy, may occur. This tends to occur more frequently in developing countries, in contrast to developed countries where the reinfection rate is low. In these countries with high reinfection rates, a strategy targeting sources of reinfection and high-risk groups would need to be employed<sup>[12]</sup>. This is distinct from failed first line therapy, which is the focus of this review.

## REASONS FOR TREATMENT FAILURE

The contributory factors to treatment failure are multi-dimensional and complex. Host genetic factors, *H. pylori* virulent factors, antibiotic resistant *H. pylori* strains, smoking habits, compliance to therapy and duration of therapy all affect treatment outcome.

### Primary antimicrobial resistance

Primary antibiotic resistance rates are rising worldwide and have a significant negative impact on treatment results<sup>[13-17]</sup>. A meta-analysis by Fischbach and Evans<sup>[18]</sup> in 2007 showed that metronidazole resistance lowered efficacy by 18%-38% while clarithromycin resistance reduced treatment efficacy 35%-66%. The study also observed that quadruple therapy could achieve a high eradication rate over 90% in the presence of single-drug resistance but could only eradicate the infection in less than 50% of subjects with *H. pylori* strains containing dual resistance to clarithromycin and metronidazole.

Resistance patterns vary significantly between regions due to differences in epidemiology of disease prevalence, socioeconomic status and the differing patterns of antibiotics usage. Amoxicillin resistance rates are generally low in many countries like Japan, United States, Europe, and China, but studies in South Korea and Iran have shown significantly higher rates. In South Korea, Lee *et al*<sup>[19]</sup> conducted a study from 2003 to 2012 and their results showed that *H. pylori* resistance had increased for all key antibiotics; amoxicillin (from 7.1% to 18.5%), clarithromycin (from 22.9% to 37.0%), metronidazole (from 34.3% to 35.8%), tetracycline (from 18.6% to 35.2%), levofloxacin (from 5.7% to 34.6%) and moxifloxacin (5.7% to 34.6%). In Iran, Abadi *et al*<sup>[20]</sup> showed that the resistance rates for amoxicillin, clarithromycin, metronidazole and tetracycline were 23.9%, 45.2%, 65.5% and 37.1% respectively. Metronidazole resistance rates are significantly higher in China and Malaysia. In Southeast China, Su *et al*<sup>[21]</sup> collected 17731 samples of antral mucosal biopsies from 2010 to 2012 and found that *H. pylori* resistance rates to amoxicillin, clarithromycin, metronidazole and levofloxacin were 0.1%, 21.5%, 95.4% and 20.6% respectively. In the more affluent and developed Beijing, Liu *et al*<sup>[22]</sup> conducted a smaller study with 73 isolated *H. pylori* strains from children, this revealed the same low

amoxicillin resistance (0), a much higher clarithromycin resistance of 84.9% and a metronidazole resistance rate of 61.6%. At the University of Malaysia Medical Centre, Goh *et al*<sup>[23]</sup> noted that metronidazole resistance had risen significantly from 10.2% in 1992 to 75.5% in 2009 and postulated that this may be due to the common prescription of metronidazole for diarrheal diseases in Malaysia. Conversely, the same study showed a very low clarithromycin resistance rate (0) in stark contrast to reports from many other countries. In Japan, Horiki *et al*<sup>[24]</sup> found that primary clarithromycin resistance rates had increased from 1.8% in 1996 to 27.1% in 2008; the overall amoxicillin resistance remained low at 0.03%. Japan has tighter regulations on the usage of metronidazole, and has an overall lower metronidazole resistance rate of 12.4% which showed no significant increase from 1996 to 1999 in a study conducted by Kato *et al*<sup>[25]</sup>. A study by Megraud *et al*<sup>[26]</sup> published in 2013 showed that the overall prevalence of resistance in 18 European countries to clarithromycin, levofloxacin, amoxicillin, tetracycline, rifabutin and metronidazole resistance rates were 17.5%, 14.1%, 0.7%, 0.9%, 1.1% and 34.9% respectively. Children had higher clarithromycin resistance (31.8%) and lower resistance rates for the other antibiotics. Adults residing in Northern Europe tend to have lower resistance rates for clarithromycin (7.7%), levofloxacin (7.7%) and metronidazole (28.6%).

Clinicians should be informed about the primary antimicrobial resistance patterns for their local treatment population before deciding on empirical treatment. In regions where antibiotic resistance is very high for key antibiotics such as amoxicillin, clinicians may consider antibiotic susceptibility testing before embarking on 2<sup>nd</sup> line treatment.

### Acid suppression

Insufficient gastric acid inhibition contributes significantly to treatment failure. A meta-analysis conducted by Villoria *et al*<sup>[27]</sup> showed that high-dose twice-daily PPI regimens had a cure rate of 88.9% while standard dose twice-daily PPI regimens had a cure rate of 81.9% in the PP analysis.

Acid-sensitive antibiotics such as clarithromycin and amoxicillin are easily degraded when the intra-gastric pH is less than 4.0. Raising intra-gastric pH from 3.5 to 5.5 increases the *in vitro* effectiveness of amoxicillin more than 10-fold<sup>[28]</sup>. Sugimoto *et al*<sup>[29]</sup> have shown that the median 24-h intra-gastric pH in patients with successful eradication on triple therapy was significantly higher compared to patients who failed therapy. Patients whose percentage time of pH < 4.0 was less than 10% and whose median 24-h pH was higher than 6.0 could eradicate the infection, even when they were infected with clarithromycin-resistant strains of *H. pylori*.

*H. pylori* can only enter the growth phase when its periplasmic pH is between 6.0 to 8.0. Therefore, adequate intra-gastric acid suppression helps to stimulate *H. pylori* to enter the growth phase and this increases its vulner-

ability to antibiotics that target its replicative cycle<sup>[30]</sup>.

Omeprazole, lansoprazole and pantoprazole are structurally very similar, and are all mainly metabolized in the liver by a genetically determined enzyme, S-mephenytoin 4'-hydroxylase (CYP2C19)<sup>[31]</sup>. In an interesting study conducted by Furuta *et al*<sup>[32]</sup>, clarithromycin-based triple therapy had the lowest eradication rate in the homozygous extensive metabolizer (EM) CYP2C19 genotype group (72.7%) compared to the heterozygous EM group (92.1%) and the poor metabolizer (PM) group (97.8%). Salvage therapy with high dose lansoprazole of 30 mg four times daily and 500 mg amoxicillin four times daily for 14 d achieved 96.8% eradication among the CYP2C19 EM genotype patients. Kang *et al*<sup>[33]</sup> also showed similar results in which EM CYP2C19 genotypes had an estimated 15% lower eradication rate compared with PM genotypes. However thus far the literature regarding the effect of CYP2C19 EM is mainly confined to clarithromycin-based triple therapy and more research is required to determine its effect in other treatment regimens<sup>[34]</sup>.

Compared to omeprazole, the bioavailability of rabeprazole was assumed to be less affected by CYP2C19 phenotype polymorphism because rabeprazole is reduced mainly *via* a non-enzymatic pathway<sup>[35]</sup>. However, reports have shown that intra-gastric pH values and plasma rabeprazole concentrations were significantly affected by CYP2C19 genotype status similar to omeprazole and the other PPIs<sup>[36,37]</sup>.

### Virulence factors of *H. pylori*

*H. pylori* strains containing a *cagA* gene produce the highly immunogenic CagA protein which is injected into the host epithelial cells, inducing a greater inflammatory response than *cagA*-negative strains, *via* interleukin 8 (IL-8) induction<sup>[38]</sup>. Studies have shown that treatment success was significantly higher in patients with more severe gastric inflammation. It was postulated that greater gastric inflammation increased the bioavailability of drugs by increasing mucosal perfusion. It has also been shown that *cagA*-positive strains grow faster compared to *cagA*-negative strains and therefore are more susceptible to antibiotics that are active during cell division<sup>[39-41]</sup>. *CagA*-positive strains also induce higher interleukin 1 $\beta$  (IL-1 $\beta$ ) and tumor necrosis factor  $\alpha$  levels in the host; both cytokines have a potent inhibitory effect on gastric acid secretion, contributing to better intra-gastric acid suppression<sup>[42,43]</sup>. Therefore, *cagA*-positive strains of *H. pylori* tend to have significantly better eradication rates.

The *vacA* gene is present in all *H. pylori* strains and different genotypes have different effects on treatment outcomes. *VacA* is a potent toxin that is secreted by *H. pylori* into the extracellular space to cause gastric epithelial cell injury. Different allele variations of *vacA* result in different levels of toxin activity; infection with strains of the *vacA* *s1* and *m1* genotypes result in higher toxin levels and greater epithelial damage and therefore more severe gastric inflammation. Similar to *cagA*, *vacA* *s1* genotypes have been shown in studies to have significantly higher

treatment success rates<sup>[44-46]</sup>.

### Host IL-1 $\beta$ polymorphism

The treatment success rates in patients with different IL-1 $\beta$  genotypes also differ; eradication rates are significantly better in IL-1B-511 T/T genotype compared to C/C and C/T genotypes<sup>[47-49]</sup>.

### Treatment duration

Treatment duration has also been investigated and studies generally show that a 10-14 d regimen is more efficacious compared to a 7-d regimen and may increase eradication rate by 4%-6%. A meta-analysis by Calvet *et al*<sup>[50]</sup> showed that 14-d regimen was significantly better than 7-d regimen in terms of ITT cure rates and, although a 10-d regimen also seemed to improve cure rates, the improvement was not significant.

### Other patient factors

In studies using 7-d standard triple therapy, lower cure rates were found in patients with a body mass index > 25 kg/m<sup>2</sup> and patients who were actively smoking; this was postulated to be due to lower drug bioavailability<sup>[51,52]</sup>. Poor compliance to therapy has a major role in treatment failure and clinicians should always enquire if patients had stopped therapy due to adverse reactions<sup>[53]</sup>.

## SECOND LINE TREATMENT OPTIONS

The Maastricht IV consensus recommended bismuth-containing quadruple therapy or levofloxacin-containing triple therapy as 2<sup>nd</sup> line treatment options<sup>[6]</sup>. This recommendation is followed across many countries, but clinicians continue to look for better eradication strategies (Table 2).

### Bismuth-containing quadruple therapy

Ang *et al*<sup>[54]</sup> evaluated the efficacy of a 7-d BQT after failure of first line clarithromycin-based triple therapy in Singapore. On ITT analysis the eradication rate was 69.8%, whereas on PP analysis, the eradication rate was 82.2%. A systemic review by Marin *et al*<sup>[55]</sup> showed that BQT had a mean eradication rate of 78% after the failure of standard clarithromycin-containing triple therapy. Its effectiveness increased with the duration of treatment, from 76% for a 7-d regimen to 82% for a 14-d regimen.

However, patient compliance may be an issue with BQT due to its complex regimen (each drug needs to be taken at different hours) and the higher incidence of adverse reactions<sup>[56]</sup>. The 3-in-1 capsule, Pylera<sup>®</sup>, which contains bismuth sub-citrate potassium (40 mg Bi203), metronidazole 125 mg and tetracycline 125 mg, still requires patients to take 3 capsules 4 times a day for 10 d with twice-daily standard dose proton pump inhibitor. Despite the pill load, the timing of drug administration is simpler and Malfertheiner *et al*<sup>[57]</sup> had reported a good compliance rate above 95%. This phase-3 trial also showed that 10-d omeprazole and Pylera was superior to 7-d clar-

**Table 2** Second and third line treatment options and study results

	Reported eradication rates in studies	Ref.	Comments
<b>Second line treatment options and study results</b>			
After failure of clarithromycin-triple therapy			
Repeat PPI, amoxicillin and clarithromycin	46% (overall)	[55]	Not recommended
PPI, amoxicillin, metronidazole	87% (overall)	[55]	Feasible in Japan with < 10% metronidazole resistance rate
	96% (ITT)	[77]	Better with extended duration <sup>1</sup>
	100% (PP)	[77]	
Bismuth-containing quadruple therapy: PPI, bismuth, tetracycline, metronidazole	78% (overall)	[55]	Better with extended duration <sup>1</sup>
	69.8% (ITT)	[54]	
	82.2% (PP)	[54]	
	84.2% (ITT)	[62]	
	92.3% (PP)	[62]	
	79.7% (ITT)	[63]	
	90.8% (PP)	[63]	
Bismuth-containing quadruple therapy: PPI, bismuth, amoxicillin, metronidazole	72% (overall)	[55]	
Bismuth-containing quadruple therapy: PPI, bismuth, tetracycline, amoxicillin	73% (overall)	[55]	
Bismuth-containing quadruple therapy: PPI, bismuth, tetracycline, amoxicillin	61.4% (overall)	[73]	
Bismuth quadruple therapy: PPI, bismuth, tetracycline, levofloxacin	78.9% (ITT)	[63]	
	87.0% (PP)	[63]	
PPI, amoxicillin and levofloxacin	76% (overall)	[55]	Better with extended duration <sup>1</sup>
	76.5% (overall)	[61]	
PPI, levofloxacin, metronidazole	67.9% (ITT)	[62]	
	73.1% (PP)	[62]	
Sequential therapy: PPI and amoxicillin for 5 d, followed by PPI, levofloxacin, nitroimidazole for 5 d	78-95% (overall)	[55]	
Moxifloxacin, PPI, amoxicillin	74.9% (overall)	[72]	14-d regimen better than 7-d regimen
	87.2% (ITT, overall)	[73]	
After failure of PPI-clarithromycin-nitroimidazole/metronidazole			
Bismuth-containing quadruple therapy: PPI, bismuth, tetracycline, metronidazole	85% (overall)	[55]	
After failure of non-bismuth quadruple therapy			
PPI, amoxicillin, levofloxacin	81% (overall)	[55]	
<b>Third line treatment options and study results</b>			
Susceptibility based selection therapy			
	88.6% (ITT and PP)	[86]	Rescue therapy was rifabutin, amoxicillin and PPI for 12 d
	90% (ITT and PP)	[86]	Rescue therapy was levofloxacin, amoxicillin and PPI for 10 d
	80.7% (ITT)	[82]	
	82.6% (PP)	[82]	
10 d sequential therapy: PPI, amoxicillin for 5 d, then PPI, levofloxacin and tetracycline for 5 d	67.23% (ITT)	[92]	
	68.38% (PP)	[92]	
Rifabutin-containing therapies	66% (55%-77%) (overall)	[84]	Rifabutin 300 mg/d dose is more effective than 150 mg/d
Rifabutin, amoxicillin, PPI	63% (overall)	[84]	
Rifaximin, levofloxacin and PPI	65%	[85]	Failed first line clarithromycin-triple therapy and second-line bismuth-containing quadruple therapy
Sitafloxacin, rabeprazole, amoxicillin	75% (ITT)	[96]	Failed first line clarithromycin-amoxicillin PPI and failed second line metronidazole-amoxicillin-PPI
	80% (PP)	[96]	
	78.2% (ITT)	[97]	
	83.6% (PP)	[97]	

<sup>1</sup>Extended duration = 10 to 14-d regimen. PPI: Proton pump inhibitor; ITT: Intention-to-treat; PP: Per protocol.

ithromycin-based triple therapy as 1<sup>st</sup>-line therapy. Another study showed that 10-d omeprazole and Pylera had similar efficacy to 10-d clarithromycin-based triple therapy<sup>[58]</sup>. Although there is limited data to show the efficacy of Pylera<sup>®</sup> in rescue therapies, a study conducted in France had shown that 10-d of omeprazole and Pylera<sup>®</sup> therapy achieved 84% eradication success in 19 patients who had failed at last 3 prior triple eradication therapies and had proven *H.*

*pylori* strains that were resistant to clarithromycin, fluoroquinolones and metronidazole<sup>[59]</sup>. Pylera<sup>®</sup> is available in the United States, France, Germany, Kuwait, Lebanon, Poland and Qatar.

### Levofloxacin-based therapy

Levofloxacin-based triple therapy is easier to administer than BQT and has a better adverse effects profile.

Levofloxacin-amoxicillin-PPI (LAP) triple regimen has a weighted mean eradication rate of 76% and a 10-d regimen yields a higher eradication rate of 84% *vs* the 69% rate of a 7-d regimen<sup>[60]</sup>. When LAP regimen was compared with BQT in a meta-analysis done by Di Caro *et al*<sup>[61]</sup>, it was found that a 7-d regimen of LAP was comparable to BQT, but a 10-d regimen of LAP was significantly better. In addition, the side effects profile was better for LAP (13.7%) compared to BQT (27.2%,  $P = 0.02$ ). Besides duration, it appears that amoxicillin is the key to the high eradication rate of the LAP combination. When Moon *et al*<sup>[62]</sup> compared levofloxacin-metronidazole-PPI with BQT in South Korea, the eradication rate in the LML group was significantly lower with only 67.9% for ITT analysis. Another study investigated if treatment efficacy will improve when the metronidazole component of BQT is replaced with levofloxacin. After failure of a clarithromycin-containing triple therapy, patients were randomised into either 10-d regimen of levofloxacin-bismuth-tetracycline-PPI or 10-d regimen of metronidazole-bismuth-tetracycline-PPI. Results showed that both therapies were equally effective and well tolerated<sup>[63]</sup>.

Levofloxacin-based therapy as second-line is also gaining more ground because more clinicians may choose to use sequential or concomitant therapies as first-line treatment when the clarithromycin resistance rate is known to be high. This means that the patients who failed such therapy had already been exposed to amoxicillin, metronidazole and clarithromycin. Going by the principle that treatment failure is due to antibiotic resistance, this leaves fewer choices for second line therapy. Gisbert *et al*<sup>[64]</sup> conducted a multicentre prospective study in which patients who failed first line non-bismuth quadruple therapy (*i.e.*, concomitant therapy or sequential therapy) were given 10 d of levofloxacin, amoxicillin and a standard dose PPI, all twice daily. The eradication rate was 75.5% (ITT) and 74% (PP) in a study population of 100 patients and tends to be higher in the treatment group who failed sequential therapy initially. Hsu *et al*<sup>[65]</sup> recently conducted an interesting multicentre study using 10-d bismuth quadruple therapy of bismuth, levofloxacin, tetracycline and PPI in 24 patients who failed sequential therapy. The study population was small but the eradication rate was encouraging at 95.8% (both ITT and PP analysis), 25% reported adverse effects mainly attributed to gastrointestinal side effects but since the adverse effects were not severe, compliance was 100%.

Despite encouraging results, the resistance rates for levofloxacin are rising as clinicians use this drug for treatment of other conditions such as pneumonia. In Asian countries, levofloxacin resistance has recently increased. For instance in South Korea, levofloxacin was 3% in 2003 and became 25.7% by 2010. In Europe where the use of levofloxacin is more controlled, fluoroquinolone resistance is lower at less than 10%<sup>[66-70]</sup>.

### Moxifloxacin-based therapy

Moxifloxacin has also been investigated as second-line

treatment; it was launched in 1999 and had higher *in vitro* activity against pathogens compared to levofloxacin. Its oral form is currently available in 123 countries. There were concerns regarding its safety profile such as tendonitis and nervous system adverse effects. However, an in depth meta-analysis has shown that moxifloxacin does not show a markedly different safety profile compared with comparator therapies (beta lactams and other quinolones)<sup>[71]</sup>.

A meta-analysis by Wu *et al*<sup>[72]</sup> compared moxifloxacin-amoxicillin-PPI (MAP) therapy to BQT and found that MAP had a higher overall eradication rate of 74.9% compared to that of BQT which was 61.4%; MAP also had a lower side effects profile. The duration of treatment in the reported studies ranged from 7 to 14 d. Miehke *et al*<sup>[73]</sup> compared 14 *vs* 7-d of esomeprazole, moxifloxacin, and amoxicillin as second-line treatment and found that the ITT eradication rate was significantly higher with 14-d (95.0%) when compared to 7-d (78.9%) therapy; however a longer duration of treatment was associated with more adverse events.

### Levofloxacin-sequential therapy as second-line

Zullo *et al*<sup>[74]</sup> first proposed the idea of sequential therapy; the regimen of PPI and amoxicillin for 5 d, followed by clarithromycin, metronidazole and PPI for the next 5 d, appeared to be more effective than standard triple therapy in 1<sup>st</sup>-line treatment. The hypothesis was that amoxicillin during the first 5 d helped to decrease the bacterial load and eliminated most of the clarithromycin-resistant strains first, the second phase of the treatment then allowed the eradication of the remaining bacteria. A multicentre clinical trial showed that levofloxacin-sequential regimen (amoxicillin and PPI for first 5 d, followed by levofloxacin, nitroimidazole and PPI for the next 5 d could achieve an eradication rate of 95.1% in the ITT analysis and 96.4% in the PP analysis if used as empirical second-line therapy. Levofloxacin resistance, as determined by the presence of *gyrA* mutations, did not appear to play a significant role in overall eradication rates. However, eradication rate was 0 in patients with dual resistance to levofloxacin and metronidazole, and 66.7% in patients sensitive to levofloxacin but resistant to metronidazole. *CYP192C* polymorphisms also had no significant impact on eradication rates; but this may be because the study used high-dose esomeprazole rather than standard-dose PPI<sup>[75]</sup>.

### Using metronidazole in second-line therapy

Some studies have shown that the “old” treatments may still work if applied in a rationale manner. After failure with clarithromycin, amoxicillin and PPI, studies have shown that 2<sup>nd</sup> line treatment with MAP may still remain feasible, especially in regions where the resistance rates to clarithromycin is high while that to metronidazole is low. Two randomised clinical trials done separately in Japan and Taiwan, which compared the efficacy of MAP with LAP, showed better results with the MAP group<sup>[76,77]</sup>. An-

other prospective study in Japan showed that 14-d regimen of MAP, with rabeprazole as the PPI, can achieve an eradication rate of 96% by ITT analysis and 100% by PP analysis, in patients who failed clarithromycin-based triple therapy<sup>[78]</sup>. The restricted use and lower resistance rates of metronidazole in Japan likely plays a big role in such study results.

## THIRD LINE TREATMENT OPTIONS

### **Treatment based on antibiotic susceptibility**

The guidelines recommend antibiotic susceptibility testing to be done in the event of two treatment failures as the choices of empirical antibiotics become much more restricted<sup>[4,6]</sup>. Studies have generally shown that using this strategy, the cumulative eradication rate after 3 lines of therapy could be 83% to 99%. The treatment should comprise of twice daily PPI and at least two sensitive antibiotics for one to two weeks. Bismuth subcitrate has also been added as a fourth agent<sup>[79,80]</sup>.

There are some disadvantages to this strategy. *H. pylori* culture requires endoscopically obtained gastric biopsy specimens, is time-consuming, costly, and the successful culture rate ranges from 75% to 90%<sup>[79-81]</sup>. Rapid molecular methods, such as polymerase chain reaction tests, may be able to speed up the detection of resistance to macrolides and fluoroquinolones, but are not widely available.

Liou *et al.*<sup>[82]</sup> showed that genotypic resistance-guided sequential therapy strategy has an overall satisfactory eradication rate of 80.7% in the ITT and 82.6% in the PP analysis. Patients who failed 2 lines of treatment were given 7 d of high-dose esomeprazole and amoxicillin, followed by high-dose esomeprazole and metronidazole and, either clarithromycin (if 23S rRNA mutation was absent), levofloxacin (if 23S rRNA mutation was present), or tetracycline (if both 23S rRNA and *gyrA* mutations were present) for another 7 d. The issue of cost-effectiveness of this treatment strategy was not discussed.

### **Rifabutin based third line treatment**

Rifabutin has very high bactericidal activity against *H. pylori* strains *in vitro*. Primary rifabutin resistance in *H. pylori* isolates is low, ranging from 1.3% to 2.4%. Unlike other antibiotics, rifabutin is chemically stable at a wide pH range and is not likely to be affected by inadequate acid suppression. A study in Spain was conducted on 92 patients who failed first line 10-d clarithromycin, amoxicillin and omeprazole therapy, failed second-line 14-d bismuth quadruple therapy, and were then given rifabutin 150mg, pantoprazole 40 mg and amoxicillin 1g twice daily. The eradication rate was 62.2% (PP analysis) and 60.8% (ITT analysis) which were sub-optimal<sup>[83]</sup>. Gisbert *et al.*<sup>[84]</sup> summarised that the overall eradication rate in 342 patients on rifabutin third-line regimen was 66%, but surprisingly the eradication rate was 70% for fourth- and fifth- line regimens suggesting that rifabutin may be used as salvage drug after multiple failures. Perri *et al.*<sup>[85]</sup> performed a randomised study in which pantoprazole, amoxicillin

and rifabutin at 150 mg daily (PAR150) for 10 d was compared with pantoprazole, amoxicillin and rifabutin 300 mg daily for 10 d (PAR300); the results was better for PAR300 with eradication rate of 87% compared to 67% in the PAR150 group. The eradication rate was higher as this was evaluated as a second-line treatment after failure of standard clarithromycin-triple therapy. Fiorini *et al.*<sup>[86]</sup> conducted a culture-based selection therapy for patients who did not respond to previous treatment for *H. pylori* infection. Patients with levofloxacin-resistant strains were given 12 d of rifabutin, amoxicillin and esomeprazole and in this scenario, the eradication rate was satisfactory at 88.6% which adds weight to the current recommendation of antibiotic susceptibility testing before choosing third line rescue therapy.

Rifabutin can cause rare but serious myelotoxicity which appears to be dose-dependent, and being a derivative of rifampicin, widespread usage may contribute to another global problem: the rising trend of multi-drug resistant tuberculosis. Suzuki *et al.*<sup>[87]</sup> has shown that a history of rifampicin usage is associated with point mutations in *rpoB* gene and high minimum inhibitory concentrations for rifabutin in *H. pylori* strains. Therefore, rifabutin should be used only as “rescue” therapy after amoxicillin, clarithromycin, metronidazole, tetracycline and levofloxacin have failed to eradicate *H. pylori*.

### **Rifaximin based third line treatment**

Compared to rifabutin, rifaximin is poorly absorbed into the blood stream and is therefore almost devoid of adverse effects and has a relatively higher bioavailability within the gastrointestinal tract<sup>[88]</sup>. However, it is unable to reach therapeutic concentrations within the gastric mucus layer, which *H. pylori* reside in due to its poor systemic adsorption. Earlier studies have generally shown poor eradication rates with Rifaximin as first line therapy of only 50%-60% regardless of combination with amoxicillin, levofloxacin or clarithromycin<sup>[89]</sup>.

However, in 2012, a study conducted in South Korea by Yun *et al.*<sup>[90]</sup> showed that rifaximin might have a role in patients who failed 2 eradication therapies. In this prospective study, 482 patients were all given first line clarithromycin-amoxicillin-pantoprazole for a week; 173 patients failed and were given tetracycline-metronidazole-bismuth-lansoprazole for 1 wk; 58 patients failed this second line treatment as well. With these 58 patients, a rescue regimen of rifaximin 200 mg trice daily, levofloxacin 500 mg once daily and lansoprazole 15 mg twice daily for 1 wk was tested; the eradication rate was 65%, the cumulative eradication rate by the time patients had reached the third-line treatment was 96%. However, in this study, treatment success was determined by one negative CUBT result after only 1 wk of stopping antibiotics or PPI, and this may lead to false negative results<sup>[91]</sup>.

### **Levofloxacin based third line treatment**

Tursi *et al.*<sup>[92]</sup> assessed the effectiveness of a third-line

levofloxacin-containing 10-d sequential treatment in 119 patients in Southern Italy. Using a sequential regimen of PPI and amoxicillin for the first 5 d, then PPI, levofloxacin and tetracycline for the remaining 5 d, eradication rates were 68.38% (PP analysis) and 67.23% (ITT analysis). Twenty-six of these patients were given levofloxacin, metronidazole and PPI as second line therapy and the eradication rate for this group was 76.92%. Overall, 24.37% of patients experienced side effects and 1.68% of patients had such severe side effects that they had to withdraw from the study. Although the patient numbers were small and the adverse reaction rate appeared high, the authors generally felt that the results was encouraging since the eradication rate was postulated to be higher if duration of therapy was 14 d instead of 10 d. Another Italian study published in 2003 used a 10-d triple therapy regimen consisting of levofloxacin 250 mg, rabeprazole 20 mg and amoxicillin 1g, all twice daily, which achieved a better eradication result of 83.3% (ITT analysis) and 88.2% (PP analysis). However this study had only 34 participants<sup>[93]</sup>.

In Japan, Murakami *et al*<sup>[94]</sup> compared third-line rescue regimens of lansoprazole and amoxicillin (LA group), lansoprazole, amoxicillin and levofloxacin (LAL group) and lansoprazole, amoxicillin and sitafloxacin (LAS group) in patients who had failed first line standard clarithromycin triple therapy and second line therapy with amoxicillin, metronidazole and PPI. The LA group had amoxicillin 500 mg four times a day, the LAL group had amoxicillin 750 mg and levofloxacin 300 mg twice daily, and the LAS group had amoxicillin 750 mg and sitafloxacin 100 mg twice daily. The LA group was treated for 14 d whereas the other 2 groups were treated for 7 d. The ITT eradication rate for both LA and LAL was dismal; only 54.3% and 43.1% respectively compared to the LAS group which was 70.0%. The disappointing results with levofloxacin may partly be explained by the high levofloxacin resistance rate of 57% in the study population. This suggests that levofloxacin-based therapy will not be effective in Japan.

### Sitafloxacin based therapy

Sitafloxacin is a novel quinolone with superior activity against *H. pylori* with *gyrA* mutations and showed better eradication rate as third line therapy compared to levofloxacin based treatment<sup>[95]</sup>. A multicentre study in Tokyo enrolled patients who failed first line clarithromycin-based triple therapy and second-line metronidazole-based triple therapy to receive empirical third-line regimen of amoxicillin 750 mg BD, sitafloxacin 100 mg BD and rabeprazole 10 mg BD for 7 d. The eradication rate was 75% by ITT analysis<sup>[96]</sup>. Another similar prospective trial conducted in Keio by Matsuzaki *et al*<sup>[97]</sup> showed that eradication rates were 83.6% by PP analysis and 78.2% by ITT analysis. These promising results suggest that sitafloxacin may be used as empirical rescue therapy with satisfactory results, however it is not widely available in many countries and its use has mainly been in Japan.

## CONCLUSION

In the event of treatment failure, the clinician should always check for poor patient compliance due to adverse reactions to the medications or patient difficulties complying with the therapy regimen. Other factors to consider would be if the patient had inadequate gastric acid-suppression or had not taken the treatment regimen for an adequate duration. An effort should be made before starting therapy to confirm if the patient had several courses of antibiotics for other infections in the past.

When first line therapy has failed, the principle is to not repeat the same antibiotics although studies have shown that amoxicillin can be “reused” as the resistance rates remain low in many countries. Clinicians need to stay vigilant to the potentially deleterious effects of rising fluoroquinolone resistance and use moxifloxacin or levofloxacin judiciously. Culture and antibiotic susceptibility testing may not be cost-effective and may delay the treatment for patients with *H. pylori* related peptic ulcer disease or MALT. However, culture and antibiotic susceptibility tests appear to be useful in selection of third-line therapy as empirical therapy have shown sub-optimal results. With the addition of newer and less invasive molecular tests to detect *H. pylori* and determine the presence of point mutations, antibiotic susceptibility tests may play a bigger role in future.

Research for the best treatment strategy is extremely challenging; there is a multitude of contributory factors to treatment failure and it will be impossible to standardise one rescue therapy internationally. Perhaps the best hope will ultimately lie in primary prevention with a vaccine using selected *H. pylori* antigens such as CagA that provides efficacious protection at the mucosal level<sup>[98]</sup>.

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