REVIEW

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Virulence factor genotypes of *Helicobacter pylori* affect cure rates of eradication therapy

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Abstract

The cure rates of *Helicobacter pylori* infection by using a combination of a proton pump inhibitor (PPI) and antimicrobial agents are mainly influenced by bacterial susceptibility to antimicrobial agents and the magnitude of acid inhibition during the treatment. Currently used empirical triple therapies do not reliably produce a ≥80% cure rate on an intention-to-treat basis. Therefore, tailored regimens based on relevant microbiological findings and pharmacogenomics are recommended for attaining an acceptable ≥95% cure rate. Recently, virulence factors of *H. pylori*, such as *cagA* and *vacA*, are reported to be major factors determining the cure rates. Individuals infected with strains with *cagA*-negative and *vacA* s2 genotypes have significantly increased risk of eradication failure of *H. pylori* infection. These virulence factors enhance gastric mucosal inflammation and are associated with the development of peptic ulcer and gastric cancer. *H. pylori* virulence factors induce proinflammatory cytokines, such as interleukin (IL)-1, IL-8, and tumor necrosis factor (TNF)-α, which influence mucosal inflammation and/or gastric acid secretion. When physicians select an *H. pylori* eradication regimen with an acceptable cure rate, they might need to consider *H. pylori* virulence factors, especially *cagA* and *vacA*.

Key words: *Helicobacter pylori*, eradication therapy, virulence factor, *cagA*, *vacA*, tailored regimen.

Abbreviations: CYP2C19 – cytochrome P450 2C19, H_2RA – histamine 2-receptor antagonist, IL – interleukin, MDR1 – multidrug resistance transporter-1, PPI – proton pump inhibitor, OipA – outer inflammatory protein, PAI – pathogenicity island, TNF – tumor necrosis factor.

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INTRODUCTION

Eradication therapy of *Helicobacter pylori* (*H. pylori)* infection is already accepted as the first-line treatment for patients with gastroduodenal disorders, such as peptic ulcer diseases, gastric mucosa associated-lymphoid tissue (MALT) lymphoma, atrophic gastritis, hyperplastic polyp, and post-endoscopic resection of early gastric cancer, as well as for patients with some extra-gastrointestinal disorders, such as idiopathic thrombocytopenic purpura, chronic idiopathic urticaria, and iron-deficiency anemia (Annibale et al. 1999; Emilia et al. 2001; Gasbarrini et al. 1998; Hopkins et al. 1996; Sugimoto et al. 2006; Take et al. 2005; Uemura et al. 1997; Uemura et al. 2001; Wong et al. 2004; Wotherspoon et al. 1994). After the cure of *H. pylori* infection, the relapse rates of peptic ulcer diseases are dramatically reduced and most peptic ulcer complications, such as hemorrhage, perforation, and abdominal symptoms, can be also dramatically prevented (Bayerdorffer et al. 1995; Hopkins et al. 1996). Eradication therapy also markedly decreases the development of gastric cancer and MALT lymphoma (Uemura 2001).

As with other bacterial infections, successful treatment of *H. pylori* infection depends on the use of antibiotics to which the organism is susceptible. Recently, the usefulness of a therapy report card, similar to that used to grade the performance of school children, was proposed, the goal of therapy being to consistently cure more than 95% of patients on an intention-to-treat basis (grade A) (Graham et al. 2007). Traditional clarithromycin-containing triple therapy with a combination of a proton pump inhibitor (PPI) (e.g. lansoprazole, omeprazole, pantoprazole, or rabeprazole), amoxicillin, and clarithromycin does not reliably produce a ≥80% cure rate, mainly due to the increased prevalence of

Table 1. Major risk factors to success of *H. pylori* eradication therapy

Risk factor		
Antibiotics	Resistant strain of *H. pylori* to antibiotics	Clarithromycin
		Metronidazole
		Levofloxacin
Acid inhibition	CYP2C19	Rapid metabolizer
	MDR1 3435	C/C genotype (Caucasian)
	IL-1B-511	C/C genotype
	IL-1B-31	T/T genotype
	Acid-inhibitory drug dosing time	Low frequency (oid)
	Acid-inhibitory drug dosing dose	Insufficient dose
H. pylori bacterial factor	*H. pylori* virulence factors	*cagA*-negative
		vacA s2 genotype
	Volume	Much
Environment factor	Smoking	Many
	Compliance	Poor

Abbreviations: CYP2C19 – cytochrome P450 2C19, IL – interleukin, MDR – multidrug resistance transporter.

clarithromycin-resistant strains (Graham et al. 2007; Graham et al. 2008). The cure rates of *H. pylori* infection are affected by several major factors, including bacterial susceptibility to antibiotics and the genotypes of host factors, such as cytochrome P450 2C19 (CYP2C19), multidrug resistance transporter-1 (MDR1), and proinflammatory cytokine polymorphisms (Table 1) (Graham et al. 2008; Megraud and Lamouliatte 2003; Sugimoto et al. 2007). Smoking habit, compliance, duration of eradication therapy, and gastric emptying have also been reported to affect the cure rates (Graham et al. 2008; Kamada et al. 1999; Megraud and Lamouliatte 2003). However, it is usually difficult to reach the excellent levels of grade A by using current regimens (see below). Therefore we need to consider other factors which increase or decrease the cure rate of *H. pylori* infection to reach the grade A.

Virulence factors of *H. pylori* (e.g. *cagA* and *vacA*) play important roles in gastric mucosal injury, such as gastric inflammation, peptic ulcer, atrophy, intestinal metaplasia, dysplasia, and malignancy (Broutet et al. 2003; van der Hulst et al. 1996). Patients with peptic ulcer diseases are reported to be more easily treated than those with non-ulcer dyspepsia; therefore, virulence factors are thought to influence the cure rates of *H. pylori* infection (Broutet et al. 2003; van der Hulst et al. 1996). In fact, the importance of *H. pylori* virulence markers in the efficacy of the cure rates has been reported (Table 2 and 3). However, the results are controversial and it is still unclear whether *H. pylori* virulence factors really influence the cure rates of *H. pylori* infection.

In this review article we first review the causes of failure for *H. pylori* eradication therapy and then summarize the effects of *H. pylori* virulence factors on *H. pylori* eradication therapy. Finally, we provide recommendations for advanced *H. pylori* eradication therapy in relation to *H. pylori* virulence factors to obtain a cure rate of grade A.

ERADICATION THERAPY AND CAUSES OF FAILURE OF *H. PYLORI* ERADICATION THERAPY

Resistance to antibiotics and H. pylori eradication therapy

Infection with antibiotic-resistant *H. pylori* strains undoubtedly influences the success or failure of *H. pylori* eradication therapy. Recently, the prevalence of clarithromycin-resistant strains has gradually increased year by year in some countries (e.g. Japan), probably due to increased usage of clarithromycin (e.g. in chronic obstructive pulmonary diseases and chronic otitis media). More than half of patients without successful eradication therapy are reported to be infected with clarithromycin-resistant strains (Furuta et al. (2001), and therefore the cure rates attained by the traditional clarithromycin-containing triple therapy is now decreasing and the traditional triple therapy remains effective only when used to treat infections with susceptible organisms (Graham et al. 2007; Graham et al. 2008). To increase the cure rates of initial treatment, currently recommended therapies include sequential therapy (sequential administration of a dual therapy [a PPI plus amoxicillin] for 5 days followed by the PPI plus clarithromycin and tinidazole or metronidazole for 5 days), bismuth-containing quadruple therapy, and therapy with a PPI plus amoxicillin, clarithromycin, and tinidazole or metronidazole for 7–14 days) (Graham et al. 2008). Amoxicillin- and tetracycline-resistant strains are both relatively rare, irrespective of the country (Adamek et al. 1998; Boyanova et al. 2008; Furuta 2001), and bismuth-resistance strains do not occur; therefore these three drugs can be key drugs in *H. pylori* eradication therapies. Similarly to clarithromycin, the prevalence of metronidazole-resistance strains is also increasing in most countries (e.g. 20–70% in some parts of Southeast Asian and European countries (Megraud

Table 2. Summary of previous studies related to *cagA* status and *H. pylori* eradication therapy

Authors	Year	Country	Diseases	Detection of *cagA*	Treatment	Definition of therapy	Cure rate (*cagA*+)	Cure rate (*cagA*–)
van der Hulst et al.	1997	Netherland	NUD, PU	PCR	OPZ+A (14)	Path, Cul	73 (89/122)*	58 (46/79)
Greenberg and Cello	1999	USA	NUD	WB	OPZ+C (14)	Path	65 (22/34)	100 (8/8)
Lopez-Brea et al.	1999	Spain	NUD, DU	PCR	PPI+AM+B	IgG, UBT	75 (6/8)	75 (18/24)
Van Doorn et al.	2000	Netherland	NUD	PCR	1. LAN (4)+BTCM			
					2. LAN (5)+BTCM	Path, RUT, Cul	70 (14/20)	44 (10/23)
			PU				87 (34/39)*	60 (9/15)
Broutet et al.	2001	France	NUD	PCR	PAN+AC	UBT, RUT, Path	81 (64/84)*	63 (45/72)
Saruc et al.	2001	Turkey	NUD	IgG	LPZ+AC	Path	87 (111/127)*	72 (41/57)
Rudi et al.	2002	Germany	NUD, PU	PCR	PPI+CA (7)			
					PPI+CM (7)	UBT, RUT	89 (73/82)	79 (26/33)
Queiroz et al.	2002	Brazil	NUD, DU	PCR	PAN+CF (7)	UBT	NA	75 (17/20)*
Scholte et al.	2002	Netherland	GERD	PCR	OPZ+AC (7)	IgG	100 (10/10)	81 (13/16)
Treiber et al.	2002	Germany	NUD, PU	PCR	1. LPZ+ACM (5)			
					2. RAN+ACM (5)			
					3. LPZ+ACM (3)	UBT	91 (147/161)	87 (61/70)
De Francesco et al.	2002	Italy	NUD	PCR	RPZ+A (5) plus RPZ+CT (5)	UBT	87 (27/31)	86 (24/28)
Chaudhuri et al.	2003	India	DU	PCR	OPX+AC (10)	RUT, Cul,Path	60 (25/42)	60 (3/5)
Russo et al.	2003	Italy	NUD, PU	PCR	LPZ+AC (7)	UBT	76 (69/91)*	42 (8/19)
Xia et al.	2003	Australia	NUD	IgG	OPZ+AC (7)	UBT, Path	88 (63/72)	NA
De Francesco et al.	2004	Italy	NUD, PU	PCR	1. RPZ+AC (10)			
					2. RPZ+A (5) plus RPZ+TC (5)	UBT	93 (68/73)*	77 (17/22)
Zhao et al.	2007	China	DU	PCR	PPI+AC (7)	RUT,Cul	93 (54/58)*	38 (3/8)

Abbreviations: cul – culture, DU – duodenal ulcer, GERD – gastroesophageal reflux disease, LPZ – lansoprazole, NA – not available, NC – not culcurate, NUD – non-ulcer dyspepsia, OPZ – omeprazole, PAN – pantoprazole, path – pathology, PPI – proton pump inhibitor, PU – peptic ulcer, RAN – ranitidine, RPZ – rabeprazole, RUT – raid urease test, UBT – urea breath test. Drugs: A – amoxicillin, B – bismuth citrate C – Calarithromycin, F – Furazolidone, M – metronidazole, TC – tetracycline, and T – tinidazole.
*$p < 0.05$ (significantly inreased cure rate compared with other group).

Table 3. Summary of previous studies related to *vacA* genotypes and eradication therapy

Authors	Year	Country	Diseases	Detection of *vacA*	Treatment	Definition of therapy	Parameter (*vacA* genotypes)	Cure rate	Cure rate (non)
Lopez-Brea et al.	1999	Spain	NUD, DU	PCR	PPI+AM+B	IgG, UBT	s1	50 (3/6)	80 (21/26)
Van Doorn et al.	2000	Netherland	NUD, PU	PCR	1. LAN (4)+BTCM				
					2. LAN (5)+BTCM	Path, RUT, Cul	s1	75 (56/75)*	50 (11/22)
Rudi et al.	2002	Germany	NUD, PU	PCR	PPI+CA (7), PPI+CM (7)	UBT, RUT	s1	87 (80/92)	83 (19/23)
							m1	90 (44/49)	83 (55/66)
Scholte et al.	2002	Netherland	GERD	PCR	OPZ+AC	IgG	s1	100 (11/11)	85 (11/13)
							m1	100 (5/5)	84 (16/19)
Chaudhuri et al.	2003	India	DU	PCR	OPZ+AC (10)	RUT, Cul,Path	s1	62 (26/42)	40 (2/5)
							m1	46 (11/24)**	74 (17/23)
Russo et al.	2003	Italy	NUD, PU	PCR	LPZ+AC (7)	UBT	s1	77 (67/97)*	43 (10/23)
De Francesco et al.	2004	Italy	NUD, PU	PCR	1. RPZ+AC (10)				
					2. RPZ+A (5) plus RPZ+TC (5)	UBT	s1	91 (40/44)	90 (46/51)
							m1	89 (33/37)	90 (52/58)
Zhao et al.	2007	China	DU	PCR	PPI+AC (7)	UBT, Cul	s1a	93 (53/57)*	44 (4/9)
							m1	94 (17/18)	83 (40/48)

Abbreviations: cul – culture, DU – duodenal ulcer, GERD – gastroesophageal reflux disease, LPZ – lansoprazole, NA – not available, NC – not calculated, NUD – non-ulcer dyspepsia, OPZ – omeprazole, PAN – pantoprazole, path – pathology, PPI – proton pump inhibitor, PU – peptic ulcer, RAN – ranitidine, RPZ – rabeprazole, RUT – raid urease test, UBT – urea breath test.

Drugs: A – amoxicillin, B – bismuth citrate, C – Calarithromycin, F – Furazolidone, M – metronidazole, TC – tetracycline, and T – tinidazole.

*$p < 0.05$ (significantly inreased cure rate compared with non-parameter group).

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1998) and regimens with increased doses of metronidazole or containing antibiotics sensitive to *H. pylori* should be routinely used in these areas.

Recently, new drugs such as fluoroquinolones (e.g. levofloxacin), furazolidone, and rifabutin have also been considered as the recommended alternative treatments (Cammarota et al. 2000; Gisbert and Morena 2006; Isomoto H, Inoue et al. 2003; Kawakami et al. 2006; Megraud 1998; Murakami et al. 2003; Nagahara et al. 2004; Saad et al. 2006; Sharara et al. 2006; Shimoyama et al. 2004). For example, the cure rates of patients with both metronidazole- and clarithromycin-resistant strains are reported to be 92% (95% CI: 83.2–96.7%) if the strains are sensitive to levofloxacin (Gatta et al. 2005). In Europe, primary resistance to levofloxacin has been reported to be infrequent (8–9.6%) (Gatta et al. 2005); therefore levofloxacin-based therapy can be used as the second-line treatment in countries where the prevalence of levofloxacin-resistant strains is low. In contrast, primary levofloxacin resistance is more common (around 15%) in Japan (Miyachi et al. 2006), so levofloxacin-based therapy might be the third-line, but not second-line, treatment option in there.

Gastric acid inhibition and H. pylori eradication therapy

Insufficient gastric acid inhibition during treatment also causes eradication failure because it makes antibiotics, especially clarithromycin and amoxicillin, more unstable and degraded in the stomach and minimizes the antimicrobial effects of antibiotics (Grayson et al. 1989; Hunt 1993). Therefore, gastric acid secretion must be potently inhibited during treatment by using acid--inhibitory drugs such as PPIs (Peterson 1997). Raising pH from 3.5 to 5.5 increases the *in vitro* effectiveness of amoxicillin more than 10-fold (Grayson et al. 1989). In fact, the 24-hour intragastric pH during eradication therapy in cured patients was significantly higher than in failure patients. It was reported that in cases in which the percentage of time of intragastric of pH<4.0 was <10% and the average 24-hour intragastric pH was <6.0 during eradication therapy, some patients could be cured of *H. pylori* infection irrespective of the bacterial susceptibility to clarithromycin (Sugimoto et al. 2007).

Recent advances in pharmacotherapeutics have demonstrated that the doses, dosing schemes, and types of acid-inhibitory drugs (PPI and/or histamine 2-receptor antagonist [H_2RA]) as well as polymorphisms of CYP2C19, *MDR1* gene, and inflammation-related cytokine genes (e.g. IL-1β and TNF-α) are influential factors contributing to gastric acid secretion during treatment. PPIs undergo extensive hepatic metabolism by the CYP system (Ishizaki and Horai 1999) and polymorphisms of CYP2C19 influence the pharmacokinetics and pharmacodynamics of PPIs (Sugimoto et al. 2004; Sugimoto et al. 2005). The cure rates of *H. pylori* infection by a triple therapy with a PPI (omeprazole 20 mg or lansoprazole 30 mg) b.i.d., amoxicillin 250 mg t.i.d., and clarithromycin 200 mg t.i.d. for one week are reported to significantly depend on CYP2C19 genotype: 72.7% in rapid metabolizers, 92.1% in intermediate metabolizers, and 97.8% in poor metabolizers (Furuta et al. 2001). The cure rates for other PPI-based eradication therapies (i.e. rabeprazole, esomeprazole, or pantoprazole) also differed among the different CYP2C19 genotype groups (Kurzawski et al. 2006; Padol et al. 2006). The cure rates in rapid metabolizers infected with clarithromycin-resistant *H. pylori* strains was dramatically low (7.1%) Furuta et al. (Furuta et al. 2001); therefore, physicians are recommended to screen CYP2C19 polymorphisms and antibiotic resistance in each patient to get a cure rate of grade A.

Inflammatory cells infiltrating into the gastric mucosa with *H. pylori* infection produce several proinflammatory cytokines. Among them, interleukin (IL)--1β and tumor necrosis factor (TNF)-α are potent inhibitors of gastric acid secretion; IL-1β is reported to be a 100-fold more potent inhibitor than PPIs and a 6000-fold more potent inhibitor than H_2RA on a molar basis (Kondo et al. 1994; Wolfe and Nompleggi 1992). Therefore the increased production of L--1β and/or TNF-α in the gastric mucosa in response to *H. pylori* infection would result in an enhanced suppression of gastric acid secretion (Furuta et al. 2002a; Furuta et al. 2002b; Takashima et al. 2001; Wang et al. 1999). *IL-1B*-511 polymorphism is associated with cure rates; cure rates in patients with the *IL-1B*-511 C/C, C/T, and T/T genotypes were reported to be 72.2% (70/97), 87.7% (164/187), and 88.2% (67/76), respectively (p=0.0017) (Furuta et al. 2004; Sugimoto et al. 2006). In contrast, there were no significant relationships between the cure rates and polymorphisms of *TNF-A*--857/-863/-1031 and *IL-10*-1082/-819/-592 (Ishida et al. 2006; Sugimoto et al. 2006). Although TNF-α potently up-regulates active inflammation by *H. pylori* infection, the acid-inhibitory effect might not be as potent as that of IL-1β (Beales and Calam 1998).

H. pylori eradication therapy and other factors

The cure rates of *H. pylori* infection are also associated with poor compliance of patients (Megraud and Lamouliatte 2003; Wermeille et al. 2002). In a meta--analysis, 14-day treatment had higher cure rates than 7-day treatment (Calvet et al. 2000); therefore the treatment period of eradication therapy may be important to the success the therapy. Poor compliance is the same as a lack-of-treatment period, and missing a few doses of drug may lead to eradication failure. Poor compliance is often due to the lack of doctors' responsibility to explain to the patients in detail about adverse events which might occur but which are usually mild and do not necessitate stopping treatment. A reliable relationship between doctor and patient should also be important for good compliance.

When determining the minimum inhibitory concentrations (MICs) of antibiotics *in vitro*, it is well known that the bacterial load can influence the cure rates of

H. pylori infection, especially for certain antibiotics such as bismuth (Megraud and Lamouliatte 2003). Several studies have confirmed that a high bacterial load plays a role in the risk of eradication failure for both standard bismuth-based triple therapy (Moshkowitz et al. 1995; Sheu et al. 1996) and one-week PPI-based triple therapy (Perri et al. 1998).

RELATIONSHIP BETWEEN *H. PYLORI* VIRULENCE FACTORS AND ERADICATION THERAPY

As with many infectious diseases, only a fraction of those infected develop clinical disease and, while this general phenomenon remains unexplained, host genetics, host immune response, and the relationships between the host response and bacterial virulence factors appear to play critical roles. Among *H. pylori* virulence factors, the functions of CagA and VacA are the most intensively studied.

cagA status and H. pylori eradication therapy

CagA is a highly immunogenic protein encoded by the *cagA* gene, located at one end of the *cag* pathogenicity island (PAI). Following injection of CagA into epithelial cells by the *cag* PAI type IV secretion system, CagA undergoes tyrosine phosphorylation at Glu-Pro--Ile-Tyr-Ala (EPIYA) motifs in the 3' region (Backert and Selbach 2008) and mimics a host cell protein by binding to and activating multiple signaling factors. *In vitro* infection experiments using gastric epithelial cells co-cultured with *H. pylori* suggest that several genes in the *cag* PAI are involved in IL-8 induction (e.g. *cagE* and *cagL*) (Al-Ghoul et al. 2004; Censini et al. 1996; Fischer et al. 2001). Until recently it was commonly thought that CagA protein *per se* was not involved in host cell gene expression, including IL-8 induction; however, recent studies suggest that CagA can be associated with IL-8 induction (in a time- and strain-dependent manner, with isogenic *cagA* mutants of some strains having reduced ability to induce IL-8) (Brandt et al. 2005). *H. pylori* is divided into *cagA*-positive and *cagA*-negative strains, and there is increasing evidence that infection with strains containing a *cagA* gene are associated with a greater inflammatory response and an increased risk of adverse clinical outcomes than infections with strains lacking the *cagA* gene in Western countries (Blaser et al. 1995; Yamaoka et al. 2006; Yamaoka et al. 2002). Interestingly, the prevalence of the *cagA*-positive strain differs among different countries, and more than 90% of *H. pylori* strains are *cagA* positive in East Asian countries, irrespective of clinical presentation (Yamaoka et al. 2002).

van der Hulst et al. (van der Hulst et al. 1997) initially reported that cure of *H. pylori* infection was achieved in a significantly greater number of patients infected with *cagA*-positive *H. pylori* (73%, 89/122) compared with those with *cagA*-negative strains (52%, 17/33; $p=0.017$; Table 2). There were many subsequent studies; eight (50.0%) out of 16 studies supported the original hypothesis and the remaining studies showed that *cagA* status was independent of the cure rate. There is no contradictory study showing increased failure risk of eradication therapy in *cagA*-positive strains.

As summarized in Table 2, each eradication regimen used different PPIs (omeprazole, lansoprazole, rabeprazole, and pantoprazole) and/or antibiotics (clarithromycin, amoxicillin, metronidazole, and tinidazole) and the duration of the treatment also varied from 3 to 14 days. However, there is no significant difference in the overall cure rates (combined *cagA*-positive and -negative) among the different studies listed in Table 2; we therefore combined the data for analysis. As a result, the cure rates in patients infected with *cagA*-positive strains were 83.1% (95% CI: 80.7–85.3%; 876/1054) and those with *cagA*-negative strains 69.9% (95% CI: 65.7–73.9%; 349/499), supporting the original hypothesis that cure rates are significantly lower in *cagA*-negative patients than in *cagA*-positive patients ($p<0.01$). Suzuki et al. (Suzuki et al. 2006) also reported that in a meta-analysis, the risk ratio for eradication failure in patients with *cagA*-negative strain (cure rate: 84%) relative to *cagA*-positive (73%) was 2.0 (95% CI: 1.6–2.4, $p<0.01$) and that *cagA* status and a high proportion of patients with non-ulcer dyspepsia were factors for heterogeneity among studies.

From a biological point, the relationship between the success or failure of *H. pylori* eradication therapy and *cagA* status has been explained by the enhanced gastric mucosal inflammation. A good correlation between *cagA* positivity and severe gastric inflammation has been confirmed (De Francesco et al. 2004; van der Hulst et al. 1997). Patients with severe inflammatory cell infiltrations in the antral mucosa were associated with significantly higher cure rates compared with those with milder inflammation (Zanten et al. 1999). Since gastric inflammation increases mucosal blood blow, it has been hypothesized that the increased blood flow may help the diffusion of antibiotics (Maeda et al. 1999). As another mechanism, *cagA*-positive strains are reported to grow faster than *cagA*-negative strains (Censini et al. 1996; van Doorn et al. 2000). Since antibiotics are active during cell division, they are more active on rapidly growing bacteria than on bacteria in resting phase.

We also hypothesize that pro-inflammatory cytokine levels should play a role in the cure rates of *H. pylori* infection. As discussed above, IL-1β is a potent inhibitor of gastric acid secretion (Kondo et al. 1994; Wolfe and Nompleggi 1992) and the increased production of IL-1β in the gastric mucosa in response to *H. pylori* infection would result in an enhanced suppression of gastric acid secretion (Furuta et al. 2002a; Furuta et al. 2002b; Takashima et al. 2001; Wang et al. 1999). The *cagA*-positive strains produce significantly higher IL--1β in gastric mucosa compared with *cagA*-negative strains (Yamaoka et al. 1996; Yamaoka et al. 1999). To

obtain a higher cure rate, gastric acid secretion should be potently inhibited during treatment and, thus, *cagA*--negative strains, which produce less IL-1β, would be less accessible to antibiotics and therefore it would be more difficult to cure *H. pylori* infection.

High *H. pylori* density in the gastric mucosa and the existence of intestinal metaplasia are reported to decrease cure rates, while a severe neutrophil infiltration is associated with significantly higher cure rates (Zhao et al. 2007). The higher *H. pylori* density in the antral mucosa enhances antral inflammation and causes lower somatostatin expression. Therefore, gastrin secretion is increased, followed by potent acid secretion, leading to the development of duodenal ulcer (Atherton et al. 1996). In general, it is well known that intestinal metaplasia has a decreased ability of acid secretion due to atrophic change in the corpus mucosa. Therefore, presence of metaplasia with atrophic change is considered to be a protective factor of eradication failure. In addition, *cagA*-positive stains are reported to be involved in the development of gastric atrophy and intestinal metaplasia (Scholte et al. 2002). However, Zhao et al. (Zhao et al. 2007) reported that intestinal metaplasia could decrease the cure rates of *H. pylori* infection and speculated that intestinal metaplasia forms a micro-environment; thus it may cause a drop in *H. pylori* cure rates. Since there is currently only one report investigating the relationship between gastric atrophy/intestinal metaplasia and cure rates (Zhao et al. 2007), further studies will be required to verify the original reports.

The prevalence of *cagA*-positive strains differs between East Asian and Western countries. In the studies listed in Table 2, the prevalence of *cagA*-positive strains is significantly higher in East Asian countries (87.9%, 58/66) than in European countries (64.9%, 848/1306; $p<0.01$). Accordingly, the cure rates in East Asian countries (86.3%, 57/66) are also significantly higher than in European countries (80.3%, 1049/1306; $p<0.01$; Table 2). To confirm the findings, further studies will be necessary to investigate whether the differences in cure rates among different geographic populations is explained by the prevalence of *cagA* status.

vacA genotypes and H. pylori eradication therapy

A single chromosomal copy of the *vacA* gene is present in essentially all *H. pylori* strains (Cover et al. 1994). *H. pylori* VacA is a potent toxin that is secreted into the extracellular space by a type V autotransporter mechanism. Gastric epithelial cell injury is caused by a vacuolating cytotoxin encoded by the *vacA* gene which induces host cell vacuolation and ultimately cell death. Specific allele variations of *vacA* exhibit different levels of toxin activity and are associated with different risks of gastrointestinal diseases. The signal (s) region of the *vacA* gene encodes part of the cytotoxin's signal peptide and N-terminus, while the middle (m) region encodes part of the 55 K C-terminal subunit. Two types of signal region (s1 and s2) and middle region (m1 and m2) exist and these cause differences in vacuolating activities among individual *H. pylori* strains (Atherton et al. 1995). The *vacA* s2 type encodes a shorter extension of the N--terminal peptide on the mature protein, which blocks the vacuolating activity (Letley and Atherton 2000). Conversely, infection with strains of the *vacA* s1 genotype has been linked to severe gastric inflammation and duodenal ulcer with enhanced cytotoxin activity. In general, *vacA* s1 and m1 genotypes produce a large amount of toxin and induce higher vacuolating activity in gastric epithelial cells, whereas s2 and m2 genotypes produce little or no toxin (Atherton et al. 1995; Letley and Atherton 2000). Accordingly, *vacA* s2–m2 strains are reported to be rarely associated with the development of peptic ulcer and gastric cancer (Atherton et al. 1995).

Several authors reported a relationship between *vacA* genotype and cure rates of *H. pylori* infection (Table 2). Three (37.5%) out of eight previous studies demonstrated significant increased risk of *H. pylori* eradication failure in *H. pylori* with *vacA* s2 genotype compared with s1 genotype (Table 2). On the other hand, there is only one study reporting a significant increased risk of eradication failure in *H. pylori* with *vacA* m1 genotype compared with m2 genotype.

Similarly to *cagA* status, each regimen used different PPIs and/or antibiotics with different duration of treatment (Table 3). However, there is no significant difference in the overall cure rates among the different studies listed in Table 3. Overall, the cure rate in patients infected with the *vacA* s1 genotypes is 79.2% (95% CI: 75.1–83.0%; 336/424) and with the *vacA* s2 genotype 72.1% (95% CI: 64.8–78.7%; 124/172; $p<0.01$). In contrast, the cure rate in patients infected with the *vacA* m1 genotype is 82.7% (95% CI: 75.1–88.7%; 110/133) and with the *vacA* m2 genotype 82.3% (95%CI: 75.8–87.6%; 144/175, $p=0.92$). These results are reasonable since clinical isolates that contain the *cagA* gene typically also have *vacA* s1 genotypes (Yamaoka et al. 2002), confirming that highly virulent strains are related to high cure rates.

Recently, a third polymorphic determinant of vacuolating activity has been described as located between the s-region and m-region, an intermediate (i) region (Rhead et al. 2007). Recent studies showed that patients infected with *vacA* i1 strains were closely associated with the development of gastric cancer in Iranian and Italian populations and of gastric ulcer in Iraqi and Italian populations (Basso et al. 2008; Hussein et al. 2008; Rhead et al. 2007). However, there is currently no report about an association between *vacA* i-region genotype and eradication therapy.

Other virulence factors and H. pylori eradication therapy

Approximately 4% of the *H. pylori* genome is predicted to encode outer membrane proteins, which may function as adhesins and contribute to pathogenesis. One such outer membrane protein is outer inflammatory protein (OipA). The functional status of the *oipA*

gene is regulated by the slipped strand repairing based on the number of CT dinucleotide repeats in the 5' region of the gene (Kudo et al. 2004; Yamaoka et al. 2002; Yamaoka et al. 2000). OipA is identified as a proinflammatory response-inducing protein given that *oipA* mutants reduced induction of IL-8 from gastric epithelial cells (Yamaoka et al. 2000). Functional OipA status is reported to be an independent determinant predictor of duodenal ulcer and is associated with high *H. pylori* density and severe neutrophil concentration (Yamaoka et al. 2002). Importantly, *oipA* functional status has been strongly correlated with the *cagA*-positive and *vacA* s1 genotype (Yamaoka et al. 2002), suggesting that *oipA* functional status should be related to higher cure rates. Since OipA is function as an adhesin (Dossumbekova et al. 2006; Yamaoka et al. 2002; Yamaoka et al. 2004), *oipA* "on" strains are expected to attach more tightly to the gastric mucosa and to be exposed to the effects of antibiotics more strongly than *oipA* "off" strains. Surprisingly, however, Treiber et al. (2002) reported that patients infected with *oipA* "off" strains (94%, 154/163) have higher cure rates compared with *oipA* "on" strains (87%, 78/88; $p<0.05$) when using the combination of lansoprazole or rabeprazole, ampicillin, clarithromycin, and metronidazole for three or five days. Since there is currently only one study investigating OipA status in eradication therapy, future studies will be necessary to investigate the relationship between OipA status and cure rates.

ASSOCIATION BETWEEN THE VIRULENCE TYPE OF *H. PYLORI* AND SUSCEPTIBILITY TO ANTIBIOTICS

There are several papers which reported a relationship between *H. pylori* antibiotic resistance patterns and virulence factor genotypes. Elviss et al. (Elviss et al. 2004) reported that susceptible isolates to clarithromycin and metronidazole were strongly associated with the *vacA* s1m2 genotype, but not with either the high-virulence *vacA* s1m1 genotype or low-virulence *vacA* s2m2genotype. However, in other papers such an association between the virulence type of *H. pylori* and susceptibility to antibiotics was not reported when the MIC values for metronidazole, amoxicillin, clarithromycin, tetracycline, and furazolidone were compared with the different *vacA*, *iceA*, *cagA*, and *cagE* genotypes (Elviss et al. 2005; Godoy et al. 2003; Loivukene et al. 2000).

DISCUSSION AND CONCLUSION

H. pylori resistance to antibiotics, insufficient acid inhibition, and *H. pylori* virulence factors are the prognostic markers of success or failure of *H. pylori* eradication therapy and can be determined by certain tests in advance of treatment. Therefore a tailored regimen based on pretreatment tests may be preferable for the achievement of higher cure rates (i.e. a grade A level). Recently, pharmacogenomics-based tailored treatment can increase the cure rates by the first-line treatment (e.g. CYP2C19-based optimization of PPI doses) (Furuta et al. 2007). In this review we also confirmed that *cagA* status and *vacA* genotypes of *H. pylori* are involved in cure rates; therefore, tailored treatment should take account of not only antibiotic resistance and CYP2C19 genotype, but also *H. pylori* virulence factors. In particular, in patients infected with low-virulence strains with *cagA*-negative and *vacA* s2 genotype, potent acid inhibition using increased doses of PPIs and/or H_2RA will be necessary for the success of eradication therapy.

To achieve cure rates of grade A, we recommend eradicating *H. pylori* infection as follows: first, physicians should check the susceptibility of *H. pylori* to antimicrobial agents before the treatment by culture and/or genetic testing and try to use antibiotics with sensitivity to *H. pylori*. Second, physicians should maintain a higher pH in the stomach in which the selected antibacterial agents become more stable and bioavailable by prescribing a frequent PPI dosage or combined dosage of PPI and H_2RA for patients who are refractory to standard PPI therapy. The dosing scheme of acid-inhibitory drugs should be optimized for each patient. Third, physicians should consider the polymorphisms of drug-metabolizing enzymes and drug transporter genes, such as CYP2C19 and *MDR1* genotypes. Finally, physicians should also check the *H. pylori* virulence factors *cagA* and/or *vacA*. When the *H. pylori* has low-virulence strains of *cagA*-negative and/or *vacA* s2 genotype, potent acid inhibition will be required for the cure of *H. pylori* infection.

Unfortunately, the above antimicrobial susceptibility test and genomic analyses for host genetics and virulence factors of *H. pylori* are not currently practical since only a few laboratories are prepared to provide the services required. However, since there are currently no definite successful regimens to achieve cure rates of grade A, a microbiological and pharmacogenomics-based tailored regimen which selects both the PPI-dosing schedule and the antibiotics according to the above-mentioned items is expected to be significantly more effective than that with the standard in the near future and all over the world.

However, before performing genotyping tests on host polymorphism and virulence factors, an analysis of cost effectiveness should be performed. Furuta et al. (Furuta et al. 2007) reported that the mean costs for successful cure of *H. pylori* per patient among a standard regimen group were almost the same as among a pharmacogenomics-based regimen group. Therefore, the pharmacogenomics-based strategy seems to be worth performing in advance since the cost of performing genotyping tests could be offset by several merits obtained from the higher cure rates by the pharmacogenomics-based treatment (Furuta et al. 2007). However,

if we combine several genotyping tests on host polymorphism and virulence factors, a high cost should be required and further studies will be necessary to investigate a more detailed cost-benefit analysis.

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