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Bismuth-containing quadruple therapy for *Helicobacter pylori*: Lessons from China

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Abstract

Objective—Antimicrobial resistance has continued to undermine many popular anti-*Helicobacter pylori* therapies. Antibiotic resistance to commonly used anti-*H. pylori* drugs in China has increased remarkably making China an ideal site to identify regimens that remain effective despite widespread antimicrobial resistance. Bismuth is one of the few antimicrobials to which resistance does not develop. Factors contributing to *H. pylori* treatment success include host factors (e.g., genetic differences in metabolism of the drugs used), bacterial factors (e.g., susceptibility) and details of the regimen (e.g., doses, dosing interval, dosing in relation of meals, formulation, etc).

Methods—We reviewed the recent experience in China with bismuth-containing quadruple therapies. The experience consists of 16 studies with 25 arms involving 1,971 patients to identify successful regimens (defined as reliably obtaining 90% or greater eradication per protocol) deserving of further study.

Results—Despite high rates of resistance to commonly used antimicrobials, several regimens were able to achieve high success. These were characteristically 14 day regimens containing a proton pump inhibitor and either tetracycline and metronidazole or furazolidone and amoxicillin.

Conclusions—We propose approaches for further development including for optimization and simplification relation to convenience and side effects (e.g., twice rather than three or 4 times daily or administration at the noon and evening meal instead of at breakfast and evening) while maintaining effectiveness 90%. Studies in China identified regimens that were highly effective despite the high prevalence of resistance to metronidazole, fluoroquinolones, and macrolides. Multicenter randomized studies will be required to confirm which is best.

Keywords

Helicobacter pylori; treatment; quadruple therapy; review; treatment success

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Conflicts of interest: Dr. Graham is a unpaid consultant for Novartis in relation to vaccine development for treatment or prevention of *H. pylori* infection. Dr. Graham is also a paid consultant for RedHill Biopharma regarding novel *H. pylori* therapies and for Otsuka Pharmaceuticals regarding diagnostic breath testing. Dr. Graham has received royalties from Baylor College of Medicine patents covering materials related to ¹³C-urea breath test. Drs Lu and Zhang have no conflicts.

Introduction

Gastric inflammation has been known to be associated with peptic ulcers and with gastric cancer for at least 100 years [1–5]. Although an infectious etiology of chronic gastritis was considered in the first half of the 20th century, proof was not obtained until the 1980s following the culture of *H. pylori* by Warren and Marshall [6]. The fact that chronic gastritis had an infectious cause suggested that cure of the infection would likely cure or prevent peptic ulcer disease and gastric cancer as these diseases were known to be tightly associated with gastritis. The discovery of *H. pylori* was rapidly followed by numerous studies seeking to identify an effective and reliably curative therapy (reviewed in [7]). Progress has been slow and advances have often been temporary because of increasing antimicrobial resistance.

An optimal anti-*H. pylori* regimen is defined as one that reliably produces cure rate of 90 (preferably 95%) for treatment of susceptible organisms. Few if any anti-*H. pylori* treatment regimens have been optimized and the general lack of susceptibility data has forced clinicians to select therapy empirically. Because of the lack of susceptibility data, an optimal therapy might be defined as one that reliably achieves high cure rates (e.g., 90% or greater) irrespective of the presence of antimicrobial resistance. The first reliably effective antimicrobial regimen was a multi-drug combination consisting of bismuth subcitrate, metronidazole and tetracycline (BMT) [8,9]. It was soon recognized that the effectiveness of BMT was diminished in the presence of metronidazole resistance and further studies showed its effectiveness could be at least partially restored by the addition of a proton pump inhibitor (PPI) along with using higher doses of metronidazole and extending the duration [10–13].

Bismuth-containing quadruple therapies have been widely used in *H. pylori* therapy with many permutations of doses and durations and with variable results [14,15]. The early observations that antimicrobial doses and treatment duration were critical determinants of outcome have been repeatedly confirmed (e.g., 7 day bismuth quadruple regimens typically produce unacceptably low cure rates in areas when metronidazole resistance is 40% or greater) [13,14,16,17].

It is unknown if one bismuth preparation or formulation is superior to others. All commercially available bismuth preparations have anti-*H. pylori* activity [18] but direct comparisons between bismuth salts and formulations are lacking. Bismuth potassium citrate, colloidal bismuth pectin, and colloidal bismuth subcitrate are available in China, where they have been widely used for treatment of diarrheas or dyspepsia. Bismuth salts are topical antimicrobials and while rarely curative as monotherapy, markedly reduce the bacterial load of *H. pylori* and apparently have synergistic effects with other antibiotics [19]. Importantly, resistance to bismuth does not develop making bismuth a preferred antimicrobial agent for treatment of *H. pylori* infections in areas where resistance to other antimicrobials is common and retreatment may be needed.

Although bismuth salts have long been used as anti-ulcer agents, bismuth preparations and formulations differ in their anti-ulcer properties. For example, colloidal bismuth subcitrate forms complexes with mucus and can coat ulcer craters. This has been suggested to protect the mucosa and ulcer base from acid-peptic attack while increasing mucosal prostaglandin synthesis and bicarbonate secretion [20]. The colloidal form of bismuth subcitrate has been shown to be effective for preventing ulceration in Shay rats whereas non-colloidal bismuth subcitrate was not [21] and studies of experimental ulcers have suggested that the ulcer-healing properties of colloidal bismuth subcitrate are not shared with bismuth subsalicylate, bismuth subcarbonate, or bismuth subnitrate [20,22]. To the best of our knowledge there are

no comparative studies on colloidal bismuth pectin. For treatment of *H. pylori* bismuth is primarily used as a topical antimicrobial and it is unclear whether its anti-ulcer properties are also important. Because the preparations appear similar in terms of *H. pylori* eradication, one would expect not.

Chinese *H. pylori* treatment guidelines recommend bismuth-containing quadruple therapies for both first-line and rescue treatments for *H. pylori* infection. Here, we summarize the effectiveness of bismuth-containing quadruple regimens that have been tested in China and where possible compare the results to local *H. pylori* resistance patterns.

Methods

This is a narrative review of the bismuth-containing quadruple therapy in China. Eligible articles were identified by search of electronic databases. We included all randomized trials using bismuth-containing quadruple regimens for treatment of *H. pylori* infection in China from 2006 to 2013. The experience consisted of 16 studies with 25 arms involving 1,971 patients. The definition of a successful regimen was based on the treatment success per protocol using the grading system 95% = excellent, 90% = good, 85–89% = borderline acceptable, 85% = unacceptable. The goal of this approach was to identify regimens that have the potential for successful clinical use (i.e., those that should be studied further in different populations, in relation to antimicrobial resistance) and are also candidates for optimization in terms of doses, frequency of administration, costs, side effects while maintaining effectiveness as measure by cure rates of 90%. For exploratory studies the primary outcome is generally expressed per protocol (PP) which controls for compliance and other variables and thus provides an indication of the potential maximum success of regimen in clinical practice. In addition, the data should also be expressed as intention to treat (ITT) which includes all subjects randomized to therapy and who received at least one dose of medicine: those lost to follow-up are typically scored as treatment failures. ITT provides an estimates of a regimen's actual success in clinical practice and is the standard for randomized multicenter trials, whereas PP is the most useful for exploratory studies to develop new regimens.

H. pylori resistance to antibiotics in China

Resistance to antibiotics is the major cause of *H. pylori* treatment failure with otherwise effective antimicrobial therapy. Antimicrobial resistance in *H. pylori* has increased rapidly in China in concert with an increase in antibiotic consumption. For example, a multi-center study conducted between 2008 and 2010 in four main cities in China showed resistance rates of 69.7% for metronidazole, 37.8% for clarithromycin, 36.4% for levofloxacin, 38.2% for moxifloxacin, 4.9% for amoxicillin, and 2.3% for tetracycline [23]. In Shanghai, Sun *et al.* investigated antibiotic resistance among *H. pylori* in 2000, 2005 and 2009 [24]. During that time clarithromycin resistance increased from 8.6% to 20.7%, levofloxacin resistance increased from 10.3% to 32.5% whereas resistant to metronidazole remained high but stable between 40% and 50%. All strains tested in that study were susceptible to amoxicillin and furazolidone and only 1 strain (isolated in 2005) was resistant to tetracycline [24]. Gao *et al.* also showed that over the last 10 years, there was an increase in clarithromycin resistance from 14.8 to 65.4%, metronidazole resistance from 38.9 to 78.8%, and fluoroquinolone resistance from 27.1 to 63.5% in Beijing [25]. In Beijing, as in Shanghai, amoxicillin resistance (0.3%) and tetracycline resistance (1.2%) remain rare [25]. As expected from these data, treatment success with standard triple therapy, 10 day sequential therapy or levofloxacin-containing triple therapy were all unsatisfactory. For example, a nation-wide, multi-center clinical study showed the PP eradication rate of standard 10-day sequential therapy was only 75.2% (185/246) [26]. A study from Beijing in 2010 compared 7-day

standard triple therapy and 7-day levofloxacin-containing triple therapy and reported ITT cure rates of only 74.5% (111/149) and 78.2% (111/142) for 7-day standard triple therapy and 82.4% (122/148) and 83.0% (122/147) for levofloxacin-containing triple therapy [27]. These generally poor results suggest that clarithromycin and fluoroquinolone-containing anti-*H. pylori* triple therapy regimens should be abandoned as empiric therapies in China and only be used with prior susceptibility testing confirming the presence of susceptible strains or in low resistance areas. Given the generally low prevalence of resistance to tetracycline and the ability to partially overcome the effects of resistance by increasing the doses and duration of bismuth quadruple therapy, bismuth-containing regimens would appear to be especially useful in China.

Bismuth-containing quadruple regimens

Western experiences—In western countries, the best results with bismuth quadruple therapy in areas with moderate to high rates of metronidazole resistance (e.g., 40%) are obtained with a 10 to 14 day (14 day being preferred) regimen given 4 times a day [13,28,29]. However, several studies from Sardinia, Italy have suggested that twice a day dosing (given with lunch and the evening meals) may be as effective while also reducing the total amount of antibiotics given to one-half [30–32]. In early western studies the replacement of tetracycline by amoxicillin did not prove to be as effective as bismuth tetracycline-containing regimens [15] but may have an advantage in regions where tetracycline resistance is an issue. Substitution of clarithromycin for metronidazole proved effective in areas where clarithromycin resistance was low but one would expect its effectiveness to be limited to those areas [33]. Substitution of doxycycline for tetracycline also provided a less effective outcome and is not recommended by western investigators [34,35].

Bismuth-containing quadruple therapy in China (bismuth, tetracycline, metronidazole, PPI): There have been a number of studies of bismuth containing anti-*H. pylori* therapy in China (Table 1). Overall, the results with traditional bismuth quadruple therapy in China are consistent with western results in regions where metronidazole resistance is greater than 40% (i.e., the outcome is relatively poor unless full dose and duration therapy is used). For example, a 7-day study in Shanghai with colloidal bismuth subcitrate, 1.5 g tetracycline (750 b.i.d.) and 1,200 mg metronidazole provided low cure rates (79.1% ITT, 82.9% PP). However, prolonging the duration to 10 days was associated with an increase in cure rate (to 88.9% ITT and 90.9%–91.6% PP) [17,36]. There have been two studies with 10-day therapy, one with 220 mg bismuth potassium citrate b.i.d., 2,250 mg tetracycline and 1,500 mg metronidazole which produced 76.7% ITT and 83.3% PP [37] and one study with 220 mg bismuth potassium citrate but only b.i.d., a very high dose of tetracycline (3 g) and a low dose of metronidazole (800 mg) which also yielded poor results (59.5% ITT, 64.1% PP) [38]. However, a recent study of a 2-week bismuth-containing quadruple therapy containing a PPI and bismuth subcitrate 220 mg b.i.d., 500 mg of tetracycline and 400 mg of metronidazole both q.i.d., achieved cure rates of 93.1% [95% CI, 88.1–98.0%) PP and 87.9% [95% CI, 81.7–94.0%) ITT (39). In that study cure rates of approximately 90% were obtained despite almost universal metronidazole resistance. (39) [Table 1). These results suggest that a potentially effective regimen has been identified and interestingly, it is similar or identical to the regimen proven to be successful in the West [29].

Bismuth-furazolidone-containing quadruple therapies: Furazolidone is a monoamine oxidase inhibitor with broad antibacterial activity based on interference with bacterial enzymes. Furazolidone was used to treat peptic ulcer disease in China for many years before *H. pylori* was discovered [40]. The consensus reports in China of 2005, 2007 and 2012 all recommend furazolidone for *H. pylori* treatment [41–43].

A 2009 study compared the cure rates of one-week and two-week furazolidone (100 mg b.i.d.) and two-week higher dose furazolidone (100 mg tid) quadruple therapy. They found extending the antibiotic course to two weeks and increasing the dose of furazolidone improved the eradication rate [44]. Six treatment arms using furazolidone and amoxicillin have been reported including a nationwide multi-center, randomized, control trial investigating the efficacy of furazolidone-containing triple and quadruple therapies for *H. pylori* eradication [Table 1] [39,44–46]. As there is almost no amoxicillin and furazolidone resistance reported in China, one would expect good outcomes. The outcomes (ITT) of 10 or 14 day regimens show eradication rates of at least 85% [46]. A large, single-center, randomized study that included 424 subjects, reported that cure rates after two-weeks of high dose amoxicillin (1 g tid) and furazolidone (0.1 g t.i.d.) were as high as 95.2% (95% CI, 91.1–99.3%) PP and 99.0% (95% CI, 97.0–100%) ITT. In that comparative study eradication rates with furazolidone-containing regimens were significantly greater than with non-furazolidone regimens [39] (Table 1).

Bismuth, clarithromycin, amoxicillin PPI quadruple therapies[39,47–49]

Studies with clarithromycin are difficult to compare as the prevalence of resistance has increased rapidly. In 2007, Mu *et al.* suggested that the addition of bismuth could improve the efficacy of 7-day triple therapy [47]. A 2010 study from Shanghai evaluated a bismuth, clarithromycin, amoxicillin, PPI quadruple therapy for 7 or 14 days [49]. As expected, the highest success was with the 14 day regimen which achieved 97.4% (95% CI: 93.8%–100%) PP and 93.7% (95% CI: 88.3%–99.0%) ITT. The fact that clarithromycin resistance is high where the study was done (i.e., 18% in Shanghai) suggested that the combination of bismuth and amoxicillin alone might be sufficient in that population and a small pilot study testing that hypothesis would be of interest.

A randomized, open-label trial in four cities (eight sites) in China was performed to compare the 10-day clarithromycin, amoxicillin, PPI quadruple therapies with bismuth and ecabet sodium and although antibiotic resistance rates were not assessed the eradication rates were higher in low clarithromycin resistance area (e.g. Shanghai, 81.3% ITT and 89.7% PP) than in the high resistance area (e.g. Xi'an, 50.0% ITT and 53.6% PP) [39]. Overall, the results are consistent with the notion that clarithromycin resistance is now so common and widespread in China that its use as an empiric choice is limited.

Miscellaneous bismuth-containing quadruple regimens

Finally, there have been a number of other combinations of bismuth, a quinolone, and a third drug (amoxicillin or furazolidone) (Table 4) [44,45,50–52] that have generally reported lower than desired cure rates and none of which appear to be candidates for further development. The 10-day bismuth potassium citrate, amoxicillin and levofloxacin regimen provided poor results (e.g., 78.7% ITT and 83.8% PP), but 14-day therapy achieved good result (i.e., 94.6% PP and 87.5% ITT) [53] and speaks against the hypothesis that bismuth-amoxicillin dual therapy might be a successful regimen.

Discussion

In China antimicrobial resistance is typically high and increasing. Resistance to clarithromycin and fluoroquinolones has reached levels such that probably neither should be used as anti-*H. pylori* therapy without prior confirmation of the presence of an infection with a susceptible strain (i.e., tailored therapy). Metronidazole resistance is also high suggesting that in bismuth-containing quadruple therapy, it should only be given a full doses and for at least 10 and preferably for 14 days [13,28,39]. In contrast, resistance to tetracycline,

furazolidone, amoxicillin are generally rare to nonexistent making them ideal as components of the optimum anti-*H. pylori* regimen.

Clinically, at least one optimum regimen and an alternate are needed to ensure that all or most patients will be cured with a maximum of two regimens [54]. All of the currently effective drugs are cheap and multi-center randomized controlled trials are needed to confirm the optimal regimens in terms of doses, durations, frequency of administration and administration in relation to meals and then to compare regimens in terms of tolerability, cost, etc. For example, in the recent study with bismuth, tetracycline, metronidazole, PPI quadruple therapy, approximately 30% experienced side effects [39]. A comparison of this regimen with the Sardinian twice day (with lunch and evening meals) would be of interest in terms of outcome and side effects [30–32].

Although furazolidone is no longer available in many counties, and its use is associated with many side effects especially in relation to interactions with foods and other drugs, it is an effective regimen drug for anti-*H. pylori* therapy [39,55] and additional studies are needed to identify the optimal use of this antimicrobial. A well thought out development program followed by optimization is needed to identify the best regimen(s) [56].

Recommendations as to which regimens are best should specify all of the important details including drugs, doses, dosing intervals, dosing in relation to meals, formulation, number of administrations and duration of therapy. A review of Table 1 shows clearly how what appears to be the same therapy may yield entirely different results when the actual regimen differs in terms of one or more of these components. As a general rule 14 day regimens are to be preferred. The regimens offering the most promise for systematic development are shown bolded and identified with an “@” in Table 1. These consist of 10 or 14-day duration quadruple therapies containing bismuth, metronidazole, tetracycline, PPI or bismuth, furazolidone, amoxicillin PP. Randomized multicenter trials are needed as well as pilot studies investigating modifications especially in relation to convenience and side effects (e.g., twice rather than three or 4 times daily or administration at the noon and evening meal instead of at breakfast and evening) that maintain effectiveness (i.e., treatment success 90%).

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Table 1
Summary of bismuth-containing quadruple therapies in China. Traditional quadruple therapy

Year	City	Bismuth*	Tetracycline	Metronidazole	PPI**	Days	#	PP	ITT	Ref
2008	Shanghai	BPC 220 b.i.d.	750 b.i.d.	400 t.i.d.	P 20 b.i.d.	7	43	82.9	79.1	[17]
2008®	Shanghai	BPC 220 b.i.d.	750 b.i.d.	400 t.i.d.	P 20 b.i.d.	10	45	90.9	88.9	[17]
2010	Linqu	BPC 300 b.i.d.	750 b.i.d.	500 t.i.d.	O20 b.i.d.	10	189	83.3	76.7	[37]
2010	Shanghai	BPC 220 b.i.d.	750 b.i.d.	400 t.i.d.	P 20 b.i.d.	10	85	91.6	88.9	[36]
2012	Shanghai	BPC 220 b.i.d.	750 b.i.d.	400 t.i.d.	E 20 b.i.d.	10	42	64.1	59.5	[38]
2013®	Shanghai	BPC 220 b.i.d.	500 b.i.d.	400 t.i.d.	L30 b.i.d.	14	107	93.1	87.9	[39]

® = recommended for further development

BPC= Bismuth Potassium Citrate,

P = pantoprazole, O = omeprazole, E = esomeprazole, L = lansoprazole

Table 2

Summary of bismuth-containing quadruple therapies in China. Furazolidone-bismuth quadruple therapy

Year	City	Bismuth*	Furazolidone	Amoxicillin	PPI**	Days	#	PP	ITT	Ref
2006	Shijiazhuang	CBS220 q.i.d.	200 q.i.d.	1000 q.i.d.	O 20 b.i.d.	1	30	36.7	36.7	[45]
2009	Beijing	BPC 220 b.i.d.	100 b.i.d.	1000 b.i.d.	R 10 b.i.d.	7	20	82.0	70.0	[44]
2009	Beijing	BPC 220 b.i.d.	100 b.i.d.	1000 b.i.d.	R 10 b.i.d.	14	20	89.0	85.0	[44]
2009@	Beijing	BPC 220 b.i.d.	100 t.i.d.	1000 b.i.d.	R 10 b.i.d.	14	20	90.0	90.0	[44]
2011	7 cities	BPC 220 b.i.d.	100 b.i.d.	1000 b.i.d.	R 20 b.i.d.	7	145	88.9	82.8	[46]
2011@	7 cities	BPC 220 b.i.d.	100 b.i.d.	1000 b.i.d.	R 20 b.i.d.	10	145	91.3	86.9	[46]
2013@	Shanghai	BPC 220 b.i.d.	100 t.i.d.	1000 t.i.d.	L 30 b.i.d.	14	104	99.0	95.2	[39]

@ = recommended for further development

BPC= Bismuth Potassium Citrate, CBS= Colloidal Bismuth Subcitrate

O = omeprazole, R = Rabeprazole, L = lansoprazole

Table 3
Summary of bismuth-containing quadruple therapies in China. Traditional triple therapy plus bismuth

Year	City	Bismuth*	Clarithromycin	Amoxicillin	PPI**	Days	#	PP	ITT	Ref
2007	Beijing	BPC 220 b.i.d.	250 b.i.d.	1000 b.i.d.	L 30 b.i.d.	7	35	93.8	85.7	[47]
2010	Shanghai	BPC 220 b.i.d.	500 b.i.d.	1000 b.i.d.	O 20 b.i.d.	7	80	82.0	80.0	[49]
2010	Shanghai	BPC 220 b.i.d.	500 b.i.d.	1000 b.i.d.	O 20 b.i.d.	14	80	97.4	93.7	[49]
2011	Changsha	BPC 220 b.i.d.	500 b.i.d.	1000 b.i.d.	E 20 b.i.d.	7	67	88.7	82.1	[48]
2013	4 cities	BPC 110 b.i.d.	500 b.i.d.	1000 b.i.d.	O 20 b.i.d.	10	156	77.0	68.0	[39]

BPC= Bismuth Potassium Citrate, L = lansoprazole, O = omeprazole, E = esomeprazole

Table 4
Summary of bismuth-containing quadruple therapies in China. Bismuth quinolone quadruple

Year	City	Bismuth*	Quinolone	Other	PPI**	Days	#	PP	ITT	Ref
2006	Shanghai	BPC 220 b.i.d.	Levo200 b.i.d.	Amox 1000 b.i.d.	O 20 b.i.d.	10	33	83.8	78.7	[50]
2010	Weihai	BP 100 q.i.d.	Levo500 b.i.d.	Amox 1000 b.i.d.	R 20 b.i.d.	10	72	83.3	83.3	[51]
2011	Shanghai	BPC 220 b.i.d.	Levo200 b.i.d.	Furaz 100 b.i.d.	P 40 b.i.d.	14	68	72.6	66.2	[52]
2011	Shanghai	BPC 220 b.i.d.	Rufl 200 q.d.	Furaz 100 b.i.d.	P 40 b.i.d.	14	70	87.7	81.4	[52]
2013®	Shanghai	BPC 220 b.i.d.	Levo500 q.d.	Amox 1000 b.i.d.	L 30 b.i.d.	14	80	94.6%	87.5%	[53]

® = recommended for further development

Levo = levofloxacin, Rufl = rifloxacin, Amox = amoxicillin, Furaz = Furazolidone,

BPC = Bismuth Potassium Citrate, BP = Colloidal Bismuth Pectin, O = omeprazole, R = Rabeprazole, P = pantoprazole, L = lansoprazole,

Table 5

Summary of bismuth-containing quadruple therapies in China. Bismuth and miscellaneous antibiotics

Year	City	Bismuth*	Other 1	Other 2	PPI**	Days	#	PP	ITT	Ref
2006	Linqu	BPC 900 q.i.d.	Mtz 500 q.i.d.	Amox 2000 q.i.d.	L 60 q.d.	1	239	27.9	26.8	[57]
2007	Beijing	BPC 220 b.i.d.	Clar 250 b.i.d.	Mtz 400 b.i.d.	L 30 b.i.d.	7	33	90.0	81.8	[47]
2012	Shanghai	BPC 220 b.i.d.	Doxy 100 b.i.d.	Amox 1000 b.i.d.	E 20 b.i.d.	10	43	72.5	67.4	[38]

Amox =amoxicillin, Clar=clarithromycin, Mtz= metronidazole, Doxy= doxycycline, L = lansoprazole, BPC= Bismuth Potassium Citrate