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Safety of furazolidone-containing regimen in *Helicobacter pylori* infection: a systematic review and meta-analysis

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ABSTRACT

Objectives Furazolidone containing regimen is effectivefor *Helicobacter pylori* (*H. pylori*) infection, but its safetyremains controversial. To assess the safety of furazolidone containing regimenin *H. pylori* infection.
Design A systematic review and meta-analysis.
Data sources PubMed, Embase, Cochrane Library, Web of Science and Scopus databases were systematically searched for eligible randomised controlled trials.
Eligibility criteria Studies comparing furazolidone with non-furazolidone-containing regimen, variable durations or doses of furazolidone were included.
Data extraction and synthesis Two reviewers independently selected studies and extracted data. Primary outcomes were the risk of total adverse events (AEs), serious AEs and severe AEs, expressed as relative risk (RR) with 95% CI. Secondary outcomes contained the incidence of individual adverse symptoms, AE-related treatment discontinuation and compliance.
Results Twenty-six articles were identified from 2039 searched records, of which 14 studies (n=2540) compared furazolidone with other antibiotics. The eradication rates of furazolidone-containing regimen were higher than those of other antibiotics in both intention-to-treat (RR 1.06, 95% CI 1.01 to 1.12) and per-protocol analysis (RR 1.05, 95% CI 1.00 to 1.10). Only two serious AEs were reported in furazolidone group (2/1221, 0.16%). No significant increased risk was observed for the incidence of total AEs (RR 1.04, 95% CI 0.89 to 1.21) and severe AEs (RR 1.81, 95% CI 0.91 to 3.60). Twelve studies (n=3139) compared different durations of furazolidone, and four studies (n=343) assessed variable doses. Elevated risk of total AEs and severe AEs were only found in a high daily dose of furazolidone rather than prolonged duration. The incidence of AE-related treatment discontinuation and compliance of patients were all similar, irrespective of dose and duration adjustments.
Conclusion Furazolidone-containing regimen has a similar risk of AEs and compliance as non-furazolidone-containing regimen. A low daily dose of 200 mg is well-tolerated for 14 day regimen and should be first considered.
PROSPERO registration number CRD42019137247

Strengths and limitations of this study

- ► This review screens trials in both initial and rescue treatment for *Helicobacter pylori* infection, so that there is a considerable amount of evidence to assess the safety of furazolidone-containing regimen.
- ► Effects of duration and dose on the safety of furazolidone are also analysed.
- ► The reporting of this review strictly follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. For the main results, sample size is measured by trial sequential analysis, and quality of evidence is graded according to the GRADE (grading of recommendations assessment, development and evaluation) approach.
- ► Limitations include most studies being open-labelled and lack of data from developed countries, which restricts the generalisability of study findings.

INTRODUCTION

Helicobacter pylori infection affects up to 44.3% of the world's population.[1] Approximately 89% cases of non-cardia gastric cancer, which accounts for 78% gastric cancers, are attributed to *H. pylori*.[2 3] Early detection and eradication of *H. pylori* can prevent the progression of gastric atrophy and reduce relative risks (RRs) for developing gastric cancers.[4 5]

Facing the yearly increasing antibiotic resistance of *H. pylori* worldwide,[6] traditional antibiotic-containing therapy is no longer reliable to achieve satisfying eradication rate.[7] Additionally, failure of first-line therapy exacerbates the difficulty for rescue treatment with significantly increased clarithromycin and metronidazole resistance.[8] Therefore, it's imperative to introduce new antibiotics with low drug resistance for the current regimen. As resistance of *H. pylori* to furazolidone remains below 5% in Asia and South America,[9] it may be a key component in treatment success, especially in regions with high antibiotic resistance.

Furazolidone is a synthetic nitrofuran derivative with a broad antibacterial and antiprotozoal spectrum to treat gastrointestinal tract infections.[10] It's well-absorbed by oral administration, and was first used to treat *H. pylori* infection in 1985. [11] Few genetic mutations have been identified in *H. pylori* for its resistance, and rare cross-resistance was observed between furazolidone and other antibiotics,[10 12 13] indicating it could be a good candidate for *H. pylori* eradication. However, the availability of furazolidone was restricted in developed countries for potential genotoxic and carcinogenetic effects in animal experiments,[14–16] but further research failed to provide any fundamental clinical evidence neither from case reports nor epidemiological studies.

Meanwhile, it's still available and widely used in developing countries owing to its good cost-effectiveness. Plenty of randomised controlled trials (RCTs) have confirmed the high efficacy of furazolidone in both initial and rescue treatment.[17] A recent meta-analysis showed furazolidone was more effective than other antibiotics in the first-line quadruple therapy, with a pooled eradication rate exceeding 90% for per-protocol analysis. But up to now, there is still no definite answer to the safety of furazolidone in *H. pylori* eradication.

Herein, we systematically reviewed relevant RCTs up to date to assess the safety and compliance of furazolidone versus other antibiotic containing regimen for *H. pylori* eradication, and further evaluated its safety in variable durations and dose schemes.

METHOD

This meta-analysis was reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement,[18] and registered on PROSPERO (international prospective register of systematic reviews) with the number: CRD42019137247.

Search strategy

Systematic literature search was conducted in PubMed, Embase, Cochrane Library, Web of Science and Scopus databases from inception to June 2019. A combination of MeSH and free terms was used to identify relevant clinical trials, including Furazolidine (with variations: Nifurazolidone, Furoxone or Furazol) and *Helicobacter* (with variations: *Helicobacter pylori* and *Campylobacter pylori*), with filters of RCTs applied to all the searching results (online supplemental appendix A). Clinicaltrials.gov, GreyNet, BIOSIS Previews, OCLC FirstSearch databases were also searched for unpublished trials and consensus reports with the same strategy. Then, we emailed authors to verify the results of retrieved studies, and manually checked reference lists of reviews, letters and included articles to identify any other relevant studies.

Inclusion and exclusion criteria

Only RCTs published in English or Chinese were eligible. The inclusion criteria were as follows: (1) *H. pylori* infection was confirmed by at least one standard detection method, including urea breath test, rapid urease test, histology, culture or faecal antigen testing. (2) Studies included at least two arms of treatments comparing furazolidone with non-furazolidone-containing regimen, different treatment durations or various doses of furazolidone. (3) Studies compared furazolidone-containing therapy with placebo or proton pump inhibitor were also included. (4) Incidence of total adverse events (AEs) and serious AEs should be monitored and available for each study arm. Exclusion criteria included: (1) Studies that enrolled paediatric patients or patients with specific underlying disease. (2) Studies that used a daily dose of furazolidone over 400 mg (the highest recommended daily dose for adults). (3) Studies that compared different forms of furazolidone regimens (eg, quadruple versus triple therapy). (4) Studies that changed the dose, duration of drugs other than furazolidone or assessed additional interventions. (5) Studies with treatment duration less than 5 days or over 14 days. (6) Studies with incomplete safety data after contacting authors, including a blurry description of safety outcomes, failing to provide a separate incidence of total AEs for each study arm and lack of serious AEs recording.

Study selection

After removal of duplicates, two reviewers independently screened all the abstracts following the selection criteria to identify relevant studies. When a decision could not be made solely based on the abstract, full text was further reviewed to assess the inclusion. Any discrepancies between the two reviewers were resolved by discussion with a third reviewer.

Data extraction

Two reviewers separately used a standardised, electronic data collection form to extract all the relevant data from included studies. Primary outcomes were the incidence of total AEs and serious AEs. We adopted a definition of serious AEs from the International Council for Harmonisation (ICH) harmonised tripartite guideline E2A. [19] Serious AEs were defined as life-threatening events requiring hospitalisation or prolonged existing hospitalisation, or resulting in persistent disability and even death. When available, the severity of AEs was also extracted. Severe AEs were defined as significant limitations to daily activity and sometimes even led to drug withdrawal.[20] Secondary outcomes were the incidence of individual adverse symptoms, the incidence of AE-related treatment discontinuation and compliance. Types of individual adverse symptoms were defined by preferred terms from the Medical Dictionary for Regulatory Activities V.19.0.[21] The list of preferred terms included: gastrointestinal disorders (nausea, vomiting, diarrhoea, constipation, dyspepsia, abdominal pain, abdominal discomfort and flatulence), nervous system disorders (dizziness, somnolence, dysgeusia and headache), skin and subcutaneous tissue disorders (rash and pruritus), psychiatric disorders (anorexia and insomnia), general disorders (fatigue, fever and chills) and other specific symptoms. For analysis of

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compliance, only patients taking at least one dose of drug were included, and the acceptable compliance level was defined as >80% for general acknowledgement. Besides, additional drug interventions, collecting methods of AEs, dose and duration of regimens were extracted for further analysis. Demographic characteristics such as age, country and baseline disease status were also extracted. Any observed data differences between the two collecting forms were checked against original texts and then examined by another reviewer to minimise human errors.

Risk of bias assessment

Two reviewers independently evaluated the methodological quality of RCTs using the first version of Cochrane Collaboration Risk of Bias tool[22] with RevMan software V.5.3.5 (Nordic Cochrane Centre, Copenhagen, Denmark, 2014). When differences could not be solved by group discussions, a third reviewer was invited to make the final decision.

Data synthesis, analysis and grading of evidence

Meta-analysis was conducted using R software V.3.6.0 (R Foundation for Statistical Computing, Vienna, Austria, 2019). For pooled estimates of dichotomous outcomes, RR and 95% CI were calculated and synthesised by the Mantel-Haenszel approach. Significant p value was set at 0.05. Random effects model was preferentially applied for conservative evaluation of treatment effect size across studies. Statistical heterogeneity was assessed using both the Q test and I^2 statistic. A p value <0.1 for the Q test or I^2 value >50% indicated significant heterogeneity.[23] Then, subgroup analysis would be done to identify the possible causes. Subgroup categories included dose of furazolidone, quadruple or triple forms of regimens, country of patients, prompted collection (collecting AEs with active return visit call or interview) or passive collection of AEs (collecting AEs with written questionnaires or report cards). Risk of publication bias was assessed by funnel plots and quantified by the Egger's linear regression test[24] and the Begg's rank correlation test.[25] Trim and fill method was applied to revise existing publication bias.[26] Sensitivity analysis was performed by continuously excluding every single study in the pooled estimate, and recalculating the RR with remaining studies. The synthesised result would be considered unreliable if any obvious alterations occurred after exclusion.

For the incidence of total AEs between furazolidone and non-furazolidone-containing regimen, trial sequential analysis (TSA) was conducted to estimate the required information size using TSA viewer software V.0.9.5.10 (Copenhagen trial unit, Copenhagen, Denmark, 2016).[27 28] Besides, two investigators independently graded the quality of evidence at outcome level, following the grading of recommendations assessment, development and evaluation (GRADE) approach.[29]

RESULTS

Search results and study characteristics

As shown in figure 1, a total of 2039 records were identified, of which 100 records were further assessed for eligibility. Finally, 26 articles met the selection criteria, enrolled in the meta-analysis and were further classified into three groups for different study aims. The consistency of study selection was good between two reviewers (κ statistic=0.83). Four of 26 articles involved two comparisons. Data from these articles were separately analysed and relevant sources were listed as a single study in each comparison group.

Fourteen studies compared furazolidone with non-furazolidone-containing regimen. The pooled intention-to-treat eradication rate was significantly higher in furazolidone containing ones (RR 1.06, 95% CI 1.01 to 1.12, online supplemental figure S1a). Similar superiority was also found in the per-protocol analysis (RR 1.05, 95% CI 1.00 to 1.10, online supplemental figure S1b). Twelve studies[30] evaluated the safety of furazolidone with different treatment durations, and four studies assessed variable doses. Prolonged duration to 14 days and higher daily dose significantly elevated the treatment efficacy (RR 1.05, 95% CI 1.02 to 1.08; RR 1.23, 95% CI 1.07 to 1.43). The main characteristics of above studies are summarised in table 1.

Risk of bias across the studies

Five studies were open-labelled trials, leading to high risk for performance bias. Twenty-one studies[30] used return visits or telephone interviews to promptly collect AEs without blinding to treatment allocation, which caused a high risk in detection bias. One study partially reported moderate and severe AEs, resulting in a high risk in reporting bias. Other biasses were low or unclear in most studies (online supplemental figure S2).

Furazolidone versus non-furazolidone containing regimen

Overall safety outcomes

Fourteen studies involving 2540 patients showed furazolidone group and non-furazolidone group had a similar risk of total AEs (RR 1.04, 95% CI 0.89 to 1.21, figure 2A), with a pooled incidence rate of 19.33% (236/1,221) and 17.59% (232/1,319), respectively. Subgroup analysis by dose, duration and quadruple or triple forms of regimens also found no significant difference. Only two serious AEs were reported in furazolidone group (0.16%, 2/1,221). Both the patients received furazolidone and amoxicillin quadruple therapy, and were hospitalised for suspicion of allergy. No serious AEs were reported in non-furazolidone group. Five studies reported the incidence of severe AEs. The pooled incidence rates in the two groups were 5.82% (22/378) and 2.74% (10/365), with no significant

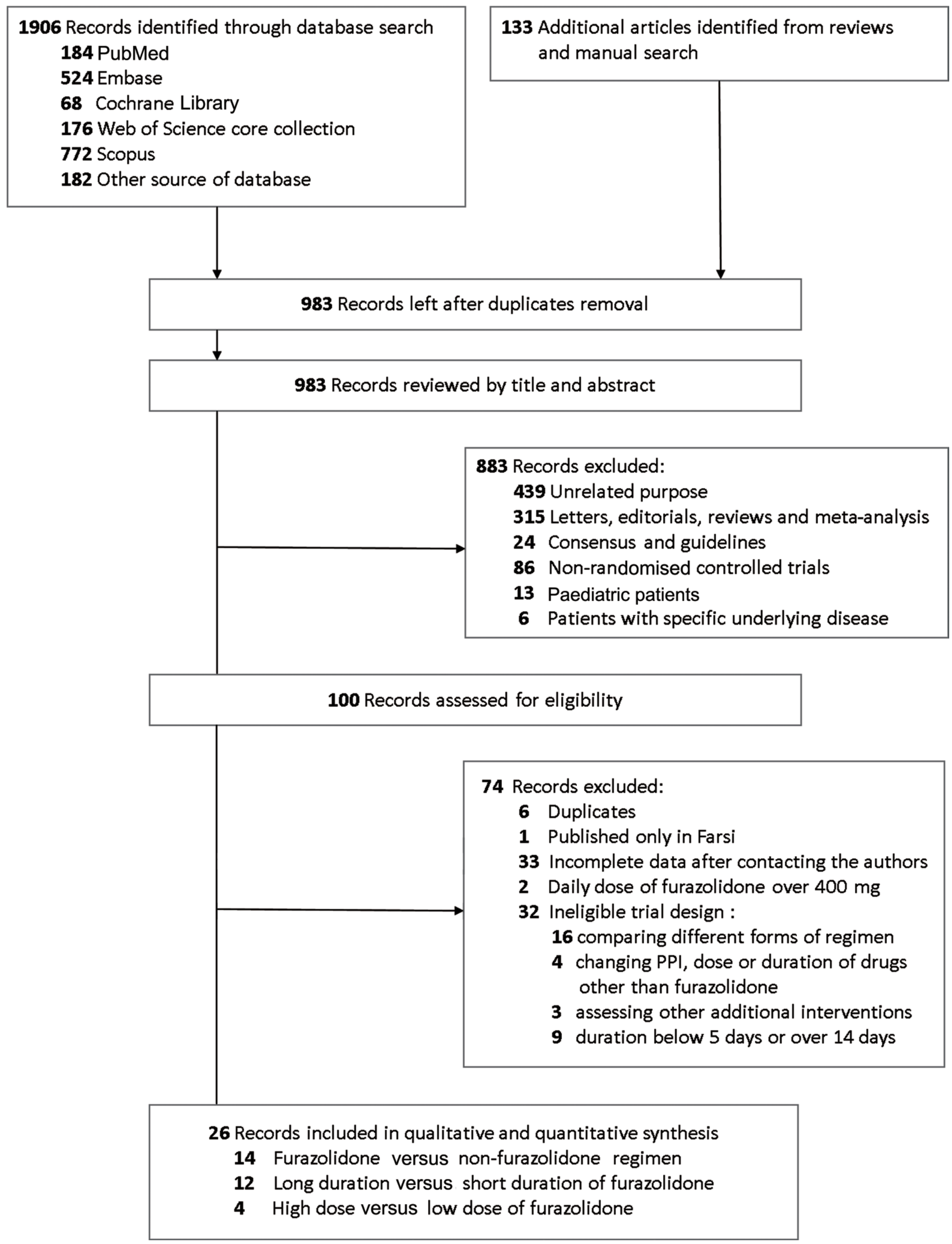

Figure 1 Flow chart for study selection. PPI, proton pump inhibitor.

increased risk detected (RR 1.81, 95% CI 0.91 to 3.60, figure 2B).

TSA analysis was performed for the incidence of total AEs between the two groups. Although the pooled population did not reach the estimated sample size, cumulative Z curve surpassed the inner futility line, indicating no significant difference would be detected even with an increased number of patients (online supplemental figure S3).

Individual adverse symptoms and compliance

Twelve studies provided detailed individual adverse symptoms, of which nausea and dizziness were commonly reported with a pooled incidence of 7.72% (74/958) vs 9.18% (90/980), 6.95% (56/806) vs 6.29% (52/827), respectively. No significant differences were found (table 2) similarly for the results of abdominal pain, diarrhoea, vomiting, headache, fever, skin rash and anorexia.

Subgroup analysis by passive reports collection even found a lower RR of nausea in furazolidone group (RR 0.42, 95% CI 0.22 to 0.79, online supplemental figure S4). However, nine studies found a higher risk of dysgeusia in non-furazolidone group (RR 0.57, 95% CI 0.35 to 0.93, table 2).

Incidence of AE-related treatment discontinuation was similar in furazolidone (3.22% (19/590)) versus non-furazolidone group (2.25% (13/577)), with a RR of 1.30

Table 1 Main characteristics of involved studies

Study, year	Country	Mean age	Indications	Furazolidone regimen	Furazolidone dose	Duration	Incidence of total AEs	Control regimen	Incidence of total AEs
Characteristics of studies compared furazolidone with non-fuazolidone containing regimen									
Liu *et al*, 1999[51]	China	44	NUD, PU	OCF	100 mg two times per day	7 days	20.00%, 7/35	OCM	22.86%, 8/35
Xiao *et al*, 1999[52]	China	44	NUD, PU	BCF	100 mg two times per day	7 days	11.67%, 7/60	BCA	5.00%, 3/60
Malekzadeh *et al*, 2000	Iran	40	PU	R[1]BAF	200 mg two times per day	14 days	26.00%, 13/50	R[1]BAM	9.62%, 5/52
Fakheri *et al*, 2001	Iran	43	NUD, PU	OBAF	200 mg two times per day	14 days	63.49%, 40/63	OBAC	58.18%, 32/55
Xiao *et al*, 2001[53]	China	44	PU	OCF	100 mg two times per day	7 days	20.09%, 46/229	OCM	20.09%, 44/219
Guo *et al*, 2004[54]	China	40	NUD, PU	OAF	100 mg two times per day	7 days	15.63%, 5/32	OAC	22.58%, 7/31
				OCF	100 mg two times per day	7 days	18.18%, 6/33	OCM	29.03%, 9/31
Zhang *et al*, 2011[55]	China	43	NUD, PU	OAF	100 mg two times per day	7 to 14 days	6.45%, 6/93	OAC	6.42%, 7/109
Zhang *et al*, 2012[56]	China	47	Not specified	ECF	100 mg three times per day	7 days	20.45%, 9/44	ECA	13.33%, 6/45
								EC L[1]	18.18%, 8/44
Chen *et al*, 2013[57]	China	41	NUD, PU	EBAF	100 mg two times per day	7 days	13.33%, 6/45	EBAC	10.42%, 5/48
Li *et al*, 2013[58]	China	42	NUD, PU	RACF	200 mg two times per day	7 days	6.67%, 2/30	RACB/Bi	3.33%, 2/60
				RACF	200 mg two times per day	14 days	13.33%, 4/30	RACB/Bi	8.33%, 5/60
Liang *et al*, 2013[59]	China	50	NUD, PU, GC	LBAF	100 mg three times per day	14 days	19.23%, 20/104	LBAT	16.19%, 17/105
				LBTF	100 mg three times per day	14 days	17.59%, 19/108	LBTM	33.64% 36/107
Zheng *et al*, 2013[60]	China	38	NUD, PU	EBAF	100 mg two times per day	10 days	11.25%, 9/80	EBAL[1]	9.21%, 7/76
Ke and Lu, 2018[61]	China	46	NUD, PU, GC	RBAF	100 mg two times per day	14 days	31.11%, 14/45	RBAC	30.23%, 13/43
				RBAF+Bi	100 mg two times per day	14 days	10.42%, 5/48	RBAC+Bi	10.87%, 5/46
Yi *et al*, 2019[62]	China	44	NUD, PU	EBAF	100 mg two times per day	14 days	19.57%, 18/92	EBAC	13.98%, 13/93
Characteristics of studies compared long duration versus short duration of furazolidone									
Wang *et al*, 2004[63]	China	43	NUD, PU	RCF	7 days	38.00%, 19/50	RCF	5 days	8.89%, 4/45
Daghaghzadeh *et al*, 2007[64]	Iran	45	NUD, PU	OBAF	14 days	38.46%, 30/78	OBAF	7 days	24.36%, 19/78

Continued

Table 1 Continued

Study, year	Country	Mean age	Indications	Furazolidone regimen	Furazolidone dose	Duration	Incidence of total AEs	Control regimen	Incidence of total AEs
Cheng and Hu, 2009[65]	China	50	NUD, PU	RBAF	14 days	15.00%, 3/20	RBAF	7 days	10.00%, 2/20
Zhang *et al*, 2011[55]	China	43	NUD	OAF	10 or 14 days	7.94%, 5/63	OAF	7 days	3.33%, 1/30
				OL[1]F	10 or 14 days	11.67%, 7/60	OL[1]F	7 days	6.67%, 2/30
Zhao and Huo, 2012[66]	China	46	NUD, PU	EAF	10 days	4.17%, 2/48	EAF	7 days	4.17%, 2/48
				EBAF	10 days	4.08%, 2/49	EBAF	7 days	6.38%, 3/47
Chen *et al*, 2013[57]	China	42	NUD, PU	EBAF	10 days	6.38%, 3/47	EBAF	7 days	13.33%, 6/45
Li *et al*, 2013[58]	China	44	NUD, PU	RACF	14 days	13.33%, 4/30	RACF	7 days	6.67%, 2/30
Zheng *et al*, 2013[60]	China	50	NUD, PU	EBAF	14 days	16.67%, 10/60	EBAF	10 days	11.86%, 7/59
Xie *et al*, 2014[67]	China	41	PU	RAF	10 days	8.33%, 15/180	RAF	7 days	8.33%, 15/180
				RBAF	10 days	9.44%, 17/180	RBAF	7 days	8.89%, 16/180
Mokhtare *et al**, 2015[68]	Iran	44	Not specified	OBAF	10 days	38.71%, 48/124	OBAM-F	5 days	29.03%, 36/124
Xu *et al*, 2015[69]	China	44	NUD, PU	PBAF	10 days	1.67%, 2/120	PBAF	7 days	1.67%, 2/120
				PAF	10 days	1.67%, 2/120	PAF	7 days	0.83%, 1/120
Xie *et al*, 2018[70]	China	44	Not specified	EBAF	10 days	9.68%, 18/186	EBAF	7 days	7.41%, 14/189
				EAF	10 days	8.02%, 15/187	EAF	7 days	7.29%, 14/192
Characteristics of studies compared high dose versus low dose of furazolidone									
Coelho *et al*, 2003[71]	Brazil	43	NUD	LCF	7 days	400 mg two times per day	17.50%, 7/40	200 mg once per day	17.95%, 7/39
Roghani *et al*, 2003[72]	Iran	38	PU	OAF	14 days	200 mg two times per day	90.48%, 57/63	50 mg two times per day	16.39%, 10/61
Fakheri *et al*, 2004[73]	Iran	46	PU	OABF	14 days	200 mg two times per day	62.00%, 31/50	100 mg two times per day	10.00%, 5/50
Cheng and Hu, 2009[65]	China	48	NUD, PU	RBAF	14 days	100 mg three times per day	30.00%, 6/20	100 mg two times per day	15.00%, 3/20

*Mokhtare *et al* was the only one study using sequential regimen. The number in the short duration column refers to the treatment length of furazolidone.
A, amoxicillin; AE, adverse events; B, bismuth; B/Bi, using bismuth or bifidobacterium in the same regimen; Bi, bifidobacterium; C, clarithromycin; E, esomeprazole; F, furazolidone; GC, gastric cancer; L[1], levofloxacin; L, lansoprazole; M, metronidazole; M-F, Metronidazole for the first 5 days followed by furazolidone for the second 5 days; NUD, non-ulcer dyspepsia; O, omeprazole; P, pantoprazole; PU, peptic ulcer; R[1], ranitidine; R, rabeprazole; T, tetracycline.;

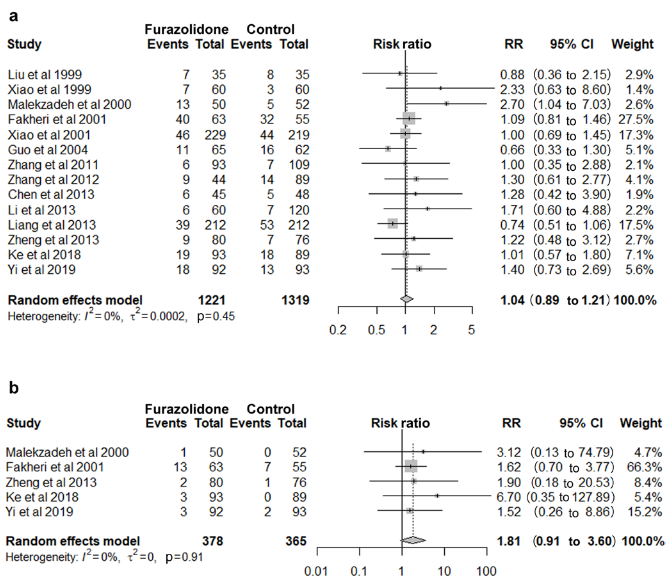

Figure 2 Furazolidone versus non-furazolidone-containing regimen: (a) Incidence of total adverse events. (b) Incidence of severe adverse events. RR, relative risk.

(95% CI 0.65 to 2.63, table 2). Patients' compliance was almost the same between two groups. (96.94% vs 96.67%, RR 1.00, 95% CI 0.99 to 1.01, table 2). Low heterogeneities were detected in these analysis.

Long duration versus short duration of furazolidone

Overall safety outcomes

Twelve studies involving 3139 patients found a higher risk of total AEs in the long-duration group (RR 1.33, 95% CI 1.09 to 1.61), which was dose-related and became non-significant with a daily dose of 200 mg (RR 1.27, 95% CI 0.92 to 1.76, figure 3). The majority of AEs were still well-tolerated, no serious AEs occurred in either group and no increased risk of severe AEs was observed (RR 1.04, 95% CI 0.38 to 2.86, table 2).

Individual adverse symptoms and compliance

Nine studies were included for analysis of individual adverse symptoms.[30] No increased risk was observed for nausea, dizziness, vomiting, diarrhoea or fatigue. Risk of AE-related treatment discontinuation and patients' compliance were also similar between the two groups. The heterogeneities were low for the above comparisons (table 2).

High dose versus low dose of furazolidone

Overall safety outcomes

Four studies with a total of 343 patients found an increased risk of total AEs in high daily dose of furazolidone (RR 3.04, 95% CI 1.28 to 7.22, figure 4A). Subgroup analysis showed similar result in a 14-day regimen with low heterogeneity (RR 4.87, 95% CI 2.89 to 8.18, figure 4A). Similarly, an elevated risk of severe AEs was observed in high-dose group (RR 3.74, 95% CI 1.29 to 10.86, figure 4B), but none of them was classified as serious AEs among all the involved patients.

Individual adverse symptoms and compliance

Data from three studies showed an obvious increased risk of nausea and dizziness in high dose versus low dose of furazolidone (RR 4.63, 95% CI 1.49 to 14.40; RR 12.28, 95% CI 2.95 to 51.07, respectively, table 2), but risk was similar for diarrhoea and headache. For analysis of compliance, a high heterogeneity arose from Roghani *et al*, 2003, which used a four-fold dose of furazolidone in the high-dose group compared with control. Subgroup analysis showed compliance was not compromised in a higher dose regimen. Risk of treatment discontinuation was also similar regardless of dosage change (table 2).

Grading of evidence

All the involved RCTs had serious study limitations for lack of allocation concealments or blinding to the treatment arms. Accordingly, the certainty of evidence was downgraded to a moderate level for most conclusions. In high dose versus low dose of furazolidone, the quality of evidence was rated low for a wide CI (table 2).

Publication bias

No publication bias were detected by the Egger's and Begg's test for the main outcomes (table 2).

Sensitivity analysis

For incidence of dysgeusia between furazolidone and non-furazolidone-containing regimen, the pooled estimates obviously shifted to a no significant level after excluding Fakheri *et al*, 2001 (online supplemental figure S5). For analysis between variable doses of furazolidone, the synthetic results were unstable for incidence of total AEs, severe AEs and nausea. But incidence of total AEs and nausea became robust to sensitivity analysis after additionally included Hosseini *et al*,[31] 2014, which compared a daily dose of furazolidone in 600 mg versus 400 mg (online supplemental figure S6).

DISCUSSION

In this meta-analysis, data of 2540 patients from 14 RCTs showed that furazolidone-containing regimen had no increased risks of total AEs or severe AEs, while maintaining higher efficacy compared with non-furazolidone-containing regimen. Only two serious AEs were reported in furazolidone group. The majority of AEs were well-tolerated with a low incidence of discontinuation and excellent compliance (>95%) to the treatment.[32]

Compared with other antibiotic regimens, furazolidone-containing regimen had superior efficacy with a similar risk of total AEs, irrespective of altered daily dose, duration and regimen forms. These results were consistent with findings in a recent meta-analysis, in which no increased risks of total AEs and severe AEs were found in seven RCTs comparing furazolidone with other antibiotic-containing regimens. The RR was 1.01 (95%CI 0.91 to 1.11) for total AEs and 1.70 (95%CI 0.84 to 3.47) for severe AEs. But these results were partially collected for

Table 2 Summary of primary and secondary outcomes

Analyses	No. of studies	No. of patients	RR (95% CI)	I^2 %	P value for heterogeneity	P value for Egger's test	P value for Begg's test	Quality of evidence (GRADE)
Furazolidone versus non-furazolidone-containing regimen								
Incidence of total AEs	14	2540	1.04 (0.89 to 1.21)	0	0.45	0.09	0.07	Moderate*
Incidence of severe AEs	5	743	1.81 (0.91 to 3.60)	0	0.91	–	–	Moderate*
Incidence of discontinuation	6	1167	1.30 (0.65 to 2.63)	0	0.80	–	–	Moderate*
Compliance	13	2373	1.00 (0.99 to 1.01)	0	0.90	0.88	0.71	Moderate*
Incidence of nausea	10	1938	0.88 (0.55 to 1.43)	52	0.03	0.39	0.93	–
Incidence of dizziness	8	1633	1.09 (0.76 to 1.57)	1	0.42	–	–	–
Incidence of dysgeusia	9	1488	0.57 (0.35 to 0.93)	15	0.31	–	–	–
Long duration versus short duration of furazolidone-containing regimen								
Incidence of total AEs	12	3139	1.33 (1.09 to 1.61)	0	0.48	0.73	0.89	Moderate*
Incidence of severe AEs	4	1003	1.04 (0.38 to 2.86)	0	0.72	–	–	–
Incidence of discontinuation	6	2477	1.22 (0.73 to 2.02)	0	0.96	–	–	–
Compliance	11	2971	1.00 (0.98 to 1.01)	0	0.48	0.89	0.82	–
High dose versus low dose of furazolidone-containing regimen								–
Incidence of total AEs	4	343	3.04 (1.28 to 7.22)	75	<0.01	–	–	Low*†[74]
Incidence of severe AEs	3	303	3.74 (1.29 to 10.86)	0	0.82	–	–	–
Incidence of discontinuation	2	224	5.37 (0.63 to 45.71)	0	0.62	–	–	–
Compliance	4	343	0.99 (0.93 to 1.06)	69	0.02	–	–	–
Incidence of nausea	3	264	4.63 (1.49 to 14.40)	0	0.69	–	–	–
Incidence of dizziness	3	264	12.28 (2.95 to 51.07)	0	0.79	–	–	–

*Downgraded by the open-label design of enrolled studies.
†Downgraded by the wide CI.
AE, adverse events; GRADE, grading of recommendations assessment, development and evaluation ; RR, relative risk.

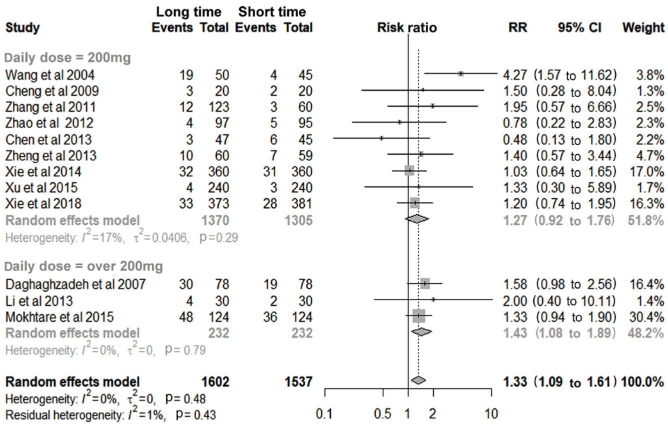

Figure 3 Long duration versus short duration of furazolidone for incidence of total adverse events.

patients with naïve infection. We additionally included patients receiving rescue treatments, designed a research strategy specialised for safety outcomes and further verified these findings. However, the quality of evidence was moderate, as most RCTs were poorly designed without allocation concealment and blinding method.

For analysis of individual adverse symptoms, no increased risks of nausea, vomiting, abdominal pain, diarrhoea, headache, fever, skin rash or anorexia were detected in patients receiving furazolidone. While, patients receiving other antibiotics were easy to have dysgeusia, which was probably caused by the wide clarithromycin use in 11 of 14 studies. But these results should be taken seriously, as sensitivity analysis detected significant alterations in the pooled estimates after excluding certain study. More evidence is required to draw a confirmed conclusion.

Additionally, we assessed the safety outcomes in variable duration and dose of furazolidone. Among patients who received a daily dose of 200 mg, no increased risk of total AEs was detected even with extended treatment duration to 14 days. When given a high daily dose of furazolidone

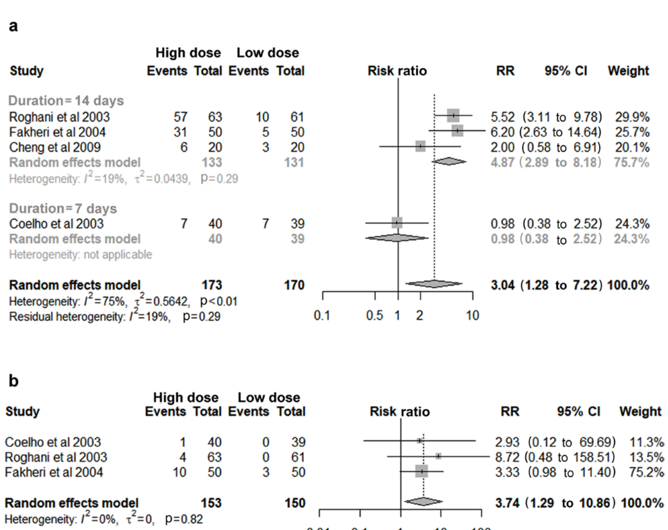

Figure 4 High dose versus low dose of furazolidone: (a) Incidence of total adverse events. (b) Incidence of severe adverse events. RR, relative risk.

ranging from 300 mg to 400mg, patients had an obvious higher risk of total AEs and severe AEs compared with the low-dose regimen. Meanwhile, the incidence of nausea and dizziness also became more frequent, which was similar with results reported by Zhuge *et al*.[33] These findings suggested that prescription of furazolidone should be started with a minimum necessary dose of 100 mg twice daily to avoid potential severe AEs. If a low-dose regimen fails to achieve expected therapeutic efficacy, extending the duration of furazolidone should be first considered rather than increasing the daily dose.

Concerns over furazolidone related irreversible AEs restricted its availability in developed countries, but up to now, no supporting clinical evidence has been reported. The International Agency for Research on Cancer (IARC) classified furazolidone as a category 3 agent with unclassifiable carcinogenicity, while metronidazole was classified as a category 2B agent with possible carcinogenicity to humans.[34] Some researchers pointed out there might be some misunderstanding of furazolidone.[35] Currently, the recommended *H. pylori* eradication schedules were 10 to 14 days. Considering the resistance to furazolidone is still rare worldwide, the benefits of short-term clinical use could easily overweigh the possible but low risk.

China has a long history use of furazolidone to cure ulcers even before the discovery of *H. pylori*. Our results showed that among 4505 patients receiving furazolidone-containing regimen in 26 trials, only two cases of serious AEs were reported with a rare incidence rate of 0.04%, which indicated the adverse reactions of furazolidone might be exaggerated in previous reviews. Both the patients received furazolidone and amoxicillin quadruple therapy, and were hospitalised for severe skin rash, flushing and abdominal colic. As allergy to penicillin is commonly reported in 10% of the population, hypersensitivity reactions to amoxicillin could not be ruled out.[36] Three patients reported numbness of limbs with suspicion of peripheral neuritis, but symptoms relieved spontaneously after stopping treatment and supplements of vitamin B1 and B6. Other severe adverse symptoms mostly disappeared after drug withdrawal without additional treatments (online supplemental table S1).

The occasionally occurring severe AEs were most likely related to the monoamine oxidase inhibitory properties of furazolidone.[37] One of its major metabolite, amino-2-oxazolidone, can non-selectively inhibit the monoamine oxidase activity, interact with metabolism of tyramine and cause dose-dependent gastrointestinal and nervous system disorders.[38] Notably, two specific AEs were reported in previous studies. One was disulfiram-like reaction to alcohol and the other was haemolytic anaemia in glucose-6-phosphate dehydrogenase (G-6-PD) deficient patients.[39] Thus, it should not be given concurrently to individuals already taking other monoamine oxidase inhibitors or antidepressants, or having decreased G-6-PD activity. Alcohol should also be avoided when furazolidone is being used.

Apart from the combination with antacids for *H. pylori* eradication, furazolidone was widely used alone for the treatment of traveller's diarrhoea, typhoid fever, cholera and *salmonella* infections. The most commonly reported AEs were gastrointestinal distress, dizziness, somnolence, headaches and general malaise.[40] In a review that quantified 191 studies, the frequency of AEs to furazolidone was 8.3% (864/10 443) in gastrointestinal infections. Most adverse symptoms were mild, with an incidence below 1%, and no drug-induced death recorded. One RCT compared furazolidone (100 mg once a day for 5 days) with ampicillin among 94 patients with traveller's diarrhoea. Only one patient receiving furazolidone dropped out due to local skin rash.[41] Another RCT assessed different doses of furazolidone in 57 children with cholera. No drug-related discontinuation of treatment occurred.[42] These data further confirm the safety of furazolidone as a single agent in treating a infectious disease.

We first evaluated the safety of furazolidone-containing regimen as a primary outcome and pointed out the increased risk of AEs was mainly attributed to the high daily dose of furazolidone. In previous meta-analyses,[43 44] safety of furazolidone regimen was only assessed as a secondary outcome, and relevant data was partially collected from RCTs eligible for efficacy analysis. Under this condition, selection bias was inevitable for incomplete data retrieval. To overcome these drawbacks, we first developed a search strategy specialised for safety evaluation, additionally included both initial and rescue treatments, and updated search scopes from 2016 to June 2019. Besides, we analysed the safety of furazoidone in variable doses and durations schemes, and first concluded a daily dose of 200 mg is safe for current 14-day eradication regimen.

This meta-analysis did have several limitations. First, most included studies did not mention allocation concealment and blinding method in the study design, which led to high detection bias of AEs reporting. Therefore, more high-quality evidence from double-blind RCTs is warranted to assess the safety outcomes accurately. Second, as the completion of treatment was around 6 to 8 weeks, incidence of delayed adverse reactions cannot be evaluated with limited follow-up duration. Finally, current conclusions are mainly based on clinical data from Asian people and developing countries. Available safety data in Western people are all from small pilot studies, and no serious AEs was observed.[45–50] More large-scale clinical trials are needed to assess the effectiveness and safety of furazolidone-containing regimen in developed countries.

In conclusion, furazolidone has similar risk of AEs as non-furazolidone-containing regimens, while maintaining good efficacy and high compliance. The majority of AEs are mild-to-moderate with a low occurrence of treatment discontinuation and excellent compliance of patients, which is not compromised by increased dose and duration of furazolidone. Higher incidence of total AEs and severe AEs for furazolidone are mainly attributed to increased dose rather than prolonged duration. A low daily dose of 200 mg is safe and well-tolerated for 14-day regimen, which should be recommended for *H. pylori* infection.

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Contributors XZ and CJ designed the study and wrote the manuscript. CJ, JL and YL collected the data and evaluated the quality of evidence. CJ analysed the data. CG, JQ and YZ helped with data interpretation and gave a critical review of the manuscript. All the authors have approved the final version of the manuscript.

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