Article

Diarrhoea Antibiotic Management using Over-the-counter Nutraceuticals in Daily practice (DIAMOND): a feasibility RCT on alternative therapy to reduce antibiotic use

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Abstract:

Background: Although rarely indicated, antibiotics are commonly used for acute diarrhoea in China. We conducted a randomized, double blind exploratory clinical trial of loperamide, berberine and turmeric for treatment of acute diarrhoea.

Methods: Adults with acute uncomplicated diarrhoea were randomized to 4 groups: (A) loperamide; (B) loperamide and berberine; (C) loperamide and turmeric; (D) loperamide, berberine and turmeric. All participants were given rescue ciprofloxacin for use after 48 hours if symptoms worsened or were unimproved. Primary endpoints were feasibility and ciprofloxacin use during the 2 week follow-up period. Semi-structured interviews were conducted following recruitment.

Results: Only 21.5% (278/1295) of patients screened were deemed eligible, and 49% (136/278) of these consented and entered into the final analysis. Most participants had mild symptoms, because most patients with moderate or severe symptoms wanted to be given antibiotics. Follow-up was good (94% at 2 weeks). Only two participants used rescue antibiotics compared to 65% of acute diarrhoea patients in the hospital during the recruitment period. The median symptom duration was: 14 hours in group B (IQR 10-22), 16 hours in group D (IQR 10-22), 18 hours in group A (IQR 10-33), 20 hours in group C (IQR 16-54). Re-consultation rates were low. There were no serious treatment-related adverse events. Most interviewed participants said the treatment was effective.

Conclusion: Although recruitment was challenging because of widespread expectations for antibiotics, patients with mild diarrhoea accepted to try an alternative. This therapy requires further evaluation in a fully powered, randomised controlled trial among a broader sample.

Trial Registration No: ChiCTR-IPR-17014107 （http://www.chictr.org.cn/index.aspx）

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Key words

Diarrhoea, Antibiotic Management,   Over-the-counter, Nutraceuticals, Feasibility RCT, Alternative therapy, Turmeric (curcumin -active ingredient)

Highlight

What is already known about this subject
- Unnecessary antibiotic use for acute diarrhoea is very common in primary care
- Patients and doctors in China expect   treatment for symptom relief
- There are safe nutraceuticals already available for acute diarrhoea treatment
- No study has evaluated if it is feasible to replace antibiotics with nutraceuticals for acute diarrhoea

What are the new findings
- It is feasible to use nutraceuticals to manage acute diarrhoea
- Patients and doctors found it acceptable to use alternatives but only for cases of mild diarrhoea
- Loperamide, berberine and turmeric as alternative therapies allowed doctors to forego antibiotics in China for patients with mild diarrhoea, but require further   evaluation in a fully powered randomised controlled trial among a broader sample

How might it impact on clinical practice in the foreseeable future
- Provide a therapeutic alternative to antibiotics for acute diarrhoea management
- After an adequately powered study, this could become standard therapy for managing acute diarrhoea

1. Introduction

Acute diarrheal disease is still a major global burden.1-3 Despite the limited benefit and potential harm from antibiotic use, acute diarrhoea is commonly treated with antibiotics in low and middle income countries (LMICs).4 Recent audits demonstrate that antibiotics are currently the standard treatment in many places in China.5 There is a clear relationship between antibiotic prescribing and antibiotic resistance,5, 6 which is a major threat to public health as new antibiotic drug development takes a long time and very significant investment.7 China is one of the highest antibiotic consuming countries, with high rates of antibiotic resistance reported.8

An effective non-antibiotic treatment for acute diarrhoea could relieve the pressure on Chinese doctors to prescribe antibiotics. Patients in primary care are often frustrated with the lack of effective interventions for self-limiting illnesses and a majority (72%) report that they expect to receive a prescription for something to help their symptoms,9 especially when they are poor and have spent precious resources to travel to see a doctor. Telling them that their problem will resolve spontaneously may lead to conflicts.10 There is thus a significant incentive for Chinese doctors to prescribe something to meet patients' satisfaction.

Non-antibiotic treatments for diarrhoea

Berberine is a natural product contained in many herbal medicines which are traditionally used for the treatment of diarrhoea.11 It is likely to be effective in acute diarrhoea,12, 13 probably working through both antibacterial and anti-inflammatory effects, protecting against lipopolysaccharide induced intestinal injury by binding to TLR4/MD-2 receptors.14, 15 Berberine use has been associated with changes in gut microbiota and an antidiarrheal effect.16 Doses up to 400mg daily were found to be effective in two trials in acute diarrhoea. 12, 13

Curcumin (from Turmeric) affects a range of cell modulating pathways and has antibacterial, antiviral, antioxidant and anti-inflammatory effects 17, 18,19. It is likely to be effective in diarrhoea of either infectious or non-infectious origin.18, 20-22 One study of curcumin showed a rapid resolution of HIV-related diarrhoea 22 at a dose of 500mg three times daily and doses up to 12000 mg per day have been used safely.20

Loperamide is a widely used anti-motility agent but also acts synergistically with antibacterial agents.23 A combination of berberine, turmeric and loperamide addresses a wide range of mechanistic pathways which are potential causes of acute diarrhoea.

Preliminary data and experience

Anecdotal experience with the combination of turmeric, berberine and loperamide for traveller's diarrhoea has yielded dramatic results in 6 participants (DB, personal communication), which is faster than would be expected by loperamide alone.24 All these agents are widely available over the counter, so this combination could provide an accessible treatment for acute diarrhoea globally and reduce inappropriate antibiotic use. However, although it is plausible that all three components are effective, it has not been clearly shown whether all three components are really needed for effective treatment. Before a fully powered trial can be justified, a smaller exploratory trial to document the feasibility and acceptability of using alternatives to antibiotics is warranted.

2. Results

Recruitment and feasibility outcomes

In total 1296 patients were screened, 1160 were excluded, and 136 were recruited. The majority of exclusions were either the doctor's assessment that the patient was too severely unwell (57%) or the patients were already on antibiotics (9%). (Figure 1)
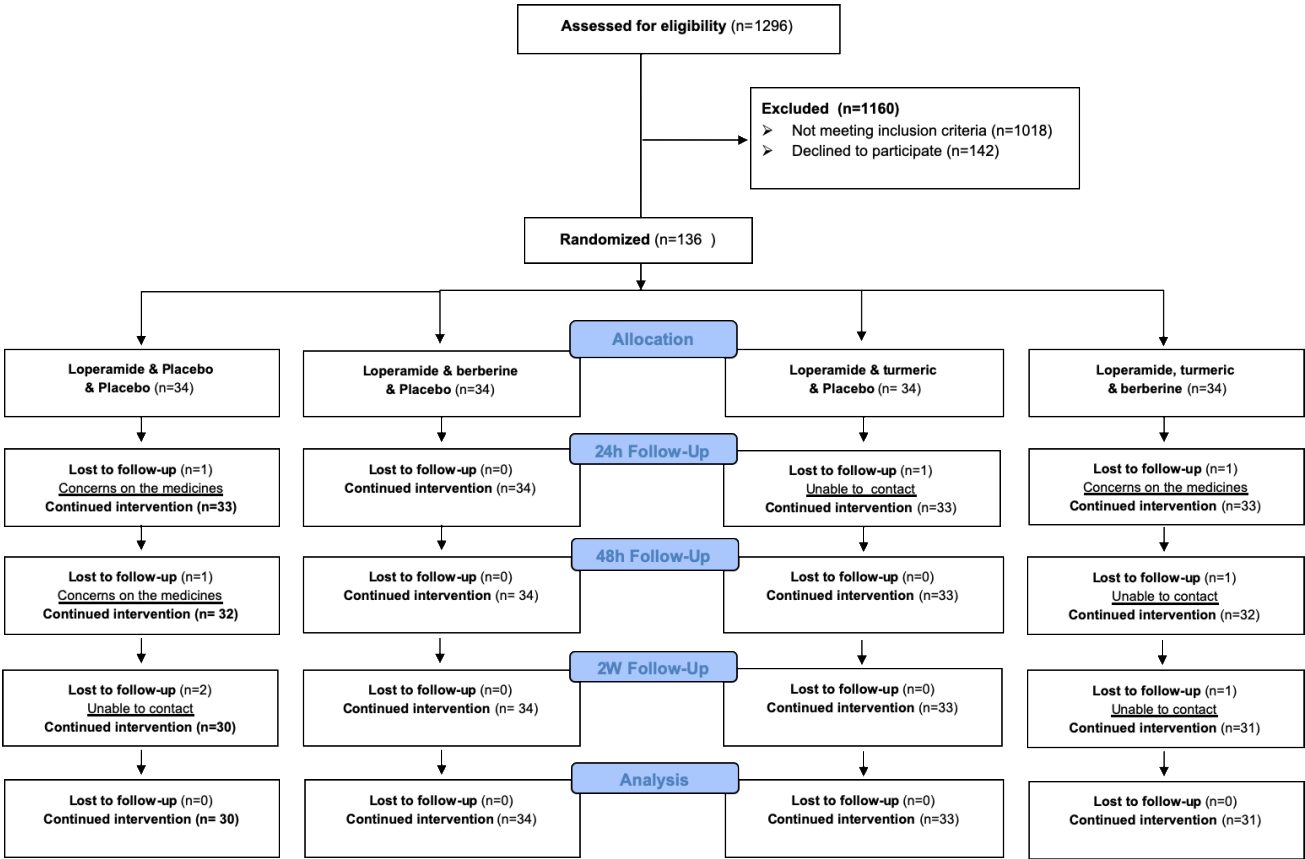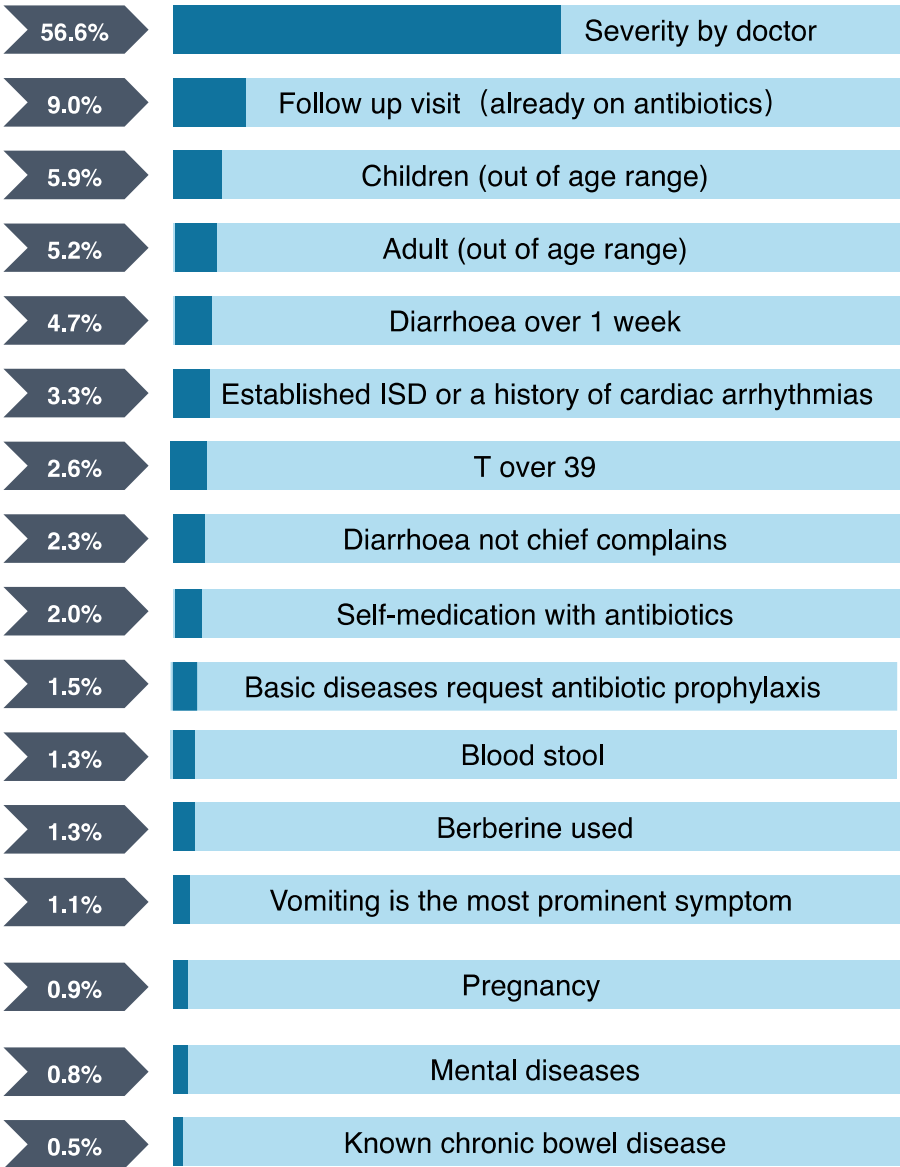
Figure 1 Consort report of patients' pathway and the reasons for declined patients.

Among the 278 eligible patients, 142 (51%) refused to participate (Figure 2); 42% gave no reason (42%), 25% did not have time, 13% did not trust the trial medicines and 11% insisted on receiving an injection (11%).

56.6%	Severity by doctor
9.0%	Follow up visit（already on antibiotics）
5.9%	Children (out of age range)
5.2%	Adult (out of age range)
4.7%	Diarrhoea over 1 week
3.3%	Established ISD or a history of cardiac arrhythmias
2.6%	T over 39
2.3%	Diarrhoea not chief complains
2.0%	Self-medication with antibiotics
1.5%	Basic diseases request antibiotic prophylaxis
1.3%	Blood stool
1.3%	Berberine used
1.1%	Vomiting is the most prominent symptom
0.9%	Pregnancy
0.8%	Mental diseases
0.5%	Known chronic bowel disease

(ISD= established ischaemic heart disease)
Figure 2. Proportion of excluded patients by reason.

Baseline characteristics

Baseline characteristics are presented in Table 1. Overall, gender was fairly balanced across randomised groups. Most patients were young or middle-aged (mean 33 years, SD 12 years), and 39% were originally from Shanghai, while the rest had migrated there for work. The median number of loose stools in the last 24 hours before treatment was 4 (IQR 4 - 5.5). Symptom severity was mild with an overall mean of 1.1 (sd 0.7) and was balanced across randomised groups. The response rate for baseline diarrhoea severity was high: among 136 recruited participants, 125 (92%) recorded diarrhoea severity. Response rates for other baseline symptom items were lower: 69 (51%) reported abdominal cramping severity, 29 (21%) reported nausea severity, and few patients (<10%) reported the remaining symptom items (vomiting, generally unwell, fever, muscle ache, headache, disturbed sleep, interference with normal activities, interference with social activities).

Table 1. Baseline characteristics

	Number	Group A Loperamide only (N=34)	Group B Loperamide+ berberine (N=34)	Group C Loperamide + turmeric (N=34)	Group D Loperamide,+ turmeric + berberine (N=34)
Gender – male (n, %)	136	18 (52.9)	20 (58.8)	17 (50.0)	22 (64.7)
Age (mean, sd)	134	33.0 (10.2)	29.9 (10.7)	34.7 (12.3)	34.0 (13.1)
Hometown - from Shanghai	136	13 (38.2)	11 (32.4)	16 (47.1)	13 (38.2)
Number loose stools in last 24h (median, IQR)	134	4.5 (4,5)	4 (3.5, 5.5)	4 (3,5)	4 (3.5, 6)
Mean symptom severity* (mean, sd)	128	0.9 (0.5)	1.3 (0.8)	1.1 (0.7)	1.1 (0.7)
Prior duration of loose stools (median, IQR)	127	19 (8,35)	13.5 (9,28)	13 (9, 33)	18 (11,30)

*Symptoms (nausea, vomiting, abdominal cramping, generally unwell, fever, muscle ache, headache, disturbed sleep, interference with normal activities, interference with social activities, diarrhoea) rated on a scale from 0 to 6, where 0 indicates no problem, 1 indicates 'very little problem', 2 indicates 'slight problem', 3 indicates 'moderately bad', 4 indicates 'bad', 5 indicates 'very bad' and 6 indicates 'as bad as it could be'

Follow-up outcomes

Follow-up rates were high, with 133 people (98%) followed up at 24 hours, 131 (96%) at 48 hours, 128 (94%) at 1 week, and 128 (94%) at 2 weeks. In total there were 8 patients who withdrew or were lost to follow up. Among those withdrawing, three were concerned with side effects from the trial medicines and 5 could not be reached after 24h or 48h (Figure 3).
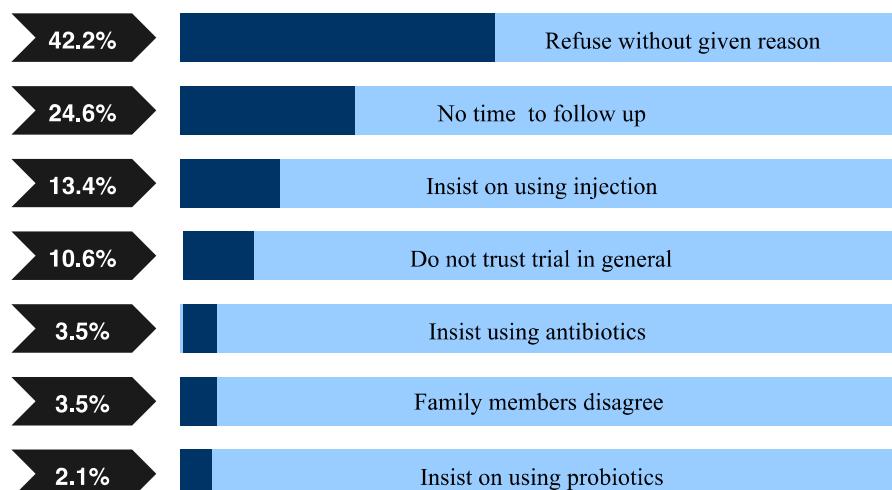

42.2% Refuse without given reason
24.6% No time to follow up
13.4% Insist on using injection
10.6% Do not trust trial in general
3.5% Insist using antibiotics
3.5% Family members disagree
2.1% Insist on using probiotics

Figure 3. Reasons for refusal to participate in the trial.

Antibiotic use

Overall only 3 participants took antibiotics during the study period. No patients in groups B (berberine + loperamide), C (turmeric + loperamide) or D (berberine & turmeric + loperamide) were

advised by a recruitment doctor to take rescue antibiotics, and 2 patients in group A (loperamide only) were advised to take rescue antibiotics. One person took rescue antibiotics in group C (loperamide & turmeric) without being advised to do so.

Effect of diarrhoea treatment on antibiotic use, duration and severity of symptoms (Table2)

Crude outcomes along with adjusted estimates for antibiotic use, duration of diarrhoea, proportion of patients with diarrhoea resolved at 24 hours and mean symptom severity during the first 48 hours are presented in Table 2. There was no statistically significant difference in duration of diarrhoea between groups, nor in the proportion of patients reporting diarrhoea resolved at 24 hours. The mean symptom severity on the 0-6 Likert scale during the first 48 hours was very mild overall and was similar across all groups.

Table 2. Effectiveness of diarrhoea treatments on antibiotic use, duration and severity of symptoms

	Number analysed	Group A Loperamide only — Crude outcome	Group B Loperamide & berberine — Crude outcome	Group B — Adjusted* OR/HR/mean difference (95% CI)	Group C Loperamide & turmeric — Crude outcome	Group C — Adjusted* OR/HR/mean difference (95% CI)	Group D Loperamide & turmeric & berberine — Crude outcome	Group D — Adjusted* OR/HR/mean difference (95% CI)
Antibiotic use (n,%)	133	2 (6.0)	0 (0.0)	-	0 (0.0)	-	0 (0.0)	-
Duration until diarrhoea resolved in hours (median, IQR)	127	18 (10, 33)	14 (10, 22)	-	20 (16, 54)	-	16 (10, 22)	-
Proportion diarrhoea resolved at 24h (n, %)	132	22 (64.7)	25 (73.5)	1.5 (0.5, 4.3)	19 (55.9)	0.7 (0.3, 1.8)	24 (70.6)	1.3 (0.5, 3.6)
Mean symptom severity during first 48h (mean, SD)	125	0.5 (0.6)	0.4 (0.4)	-0.1 (-0.4, 0.2)	0.6 (0.7)	0.1 (-0.2, 0.4)	0.5 (0.5)	0.0 (-0.3, 0.3)

*Analyses adjusted for number of loose stools at baseline, mean severity and prior duration. All mean differences, odds ratios (ORs), hazard ratios (HRs) reported in comparison with reference group A

Side-effects and re-consultations (Table 3)

No constipation was reported for groups B or C at 24 hours or 48 hours. Constipation affected a small number of patients in groups A and D, and the mean severity of constipation at 24 and 48 hours was mild. No rashes were reported at 24 or 48 hours. There were very small numbers of unscheduled re-consultations and re-contacts.

Table 3. Side effects and re-consultation

	Number analysed	Group A	Group B	Group C	Group D

		Loperamide alone	Loperamide & berberine	Loperamide & turmeric	Loperamide & turmeric & berberine
Mean severity of constipation[*] at 24h (mean, sd)	12	1.3 (0.6)	-	-	0.8 (0.4)
Mean severity of constipation at 48h (mean, sd)	6	1.0 (1.0)	-	-	1.0 (1.4)
Re-consultation (n, %)	125	1 (3.6)	1 (2.9)	0 (0.0)	1 (3.3)
Re-contact (n, %)	125	1 (3.6)	1 (2.9)	1 (3.0)	0 (0.0)

*Constipation severity rated on a scale from 0 to 6, where 0 indicates no problem, 1 indicates 'very little problem', 2 indicates 'slight problem', 3 indicates 'moderately bad', 4 indicates 'bad', 5 indicates 'very bad' and 6 indicates 'as bad as it could be'.

Usual care for acute diarrhoea

We extracted data from the hospital information system for all patients diagnosed with only acute diarrhoea without any comorbidities over the same time period. 1367 patients in the same age range were analysed. There were 757 male (55%), and 610 female (45%) patients. Mean age was 41 years old. The antibiotic use rate overall during the study period was 914 (67%) and the injectable antibiotic use rate was 64% (581/914). More than 60% were given 1 antibiotic and 38% received 2 antibiotics. 63% were given levofloxacin and 32% a 3rd generation cephalosporin.

Interview study

We attempted to contact 30 randomly selected participants for interviews via phone call. 7 participants did not answer, 6 interviews could not be completed because of connectivity problems, 3 were too busy to be interviewed. Fourteen participants were interviewed. We also interviewed six recruiting doctors (face to face) and six on-site researchers (3 by phone calls and 3 face to face, Supplemental table). All interviews lasted about 30 minutes (15-55 minutes). Thematic analysis 34 was employed for the transcripts. We identified three key themes in this study (Figure 4). Table 4 showed the detailed quotes from interview.
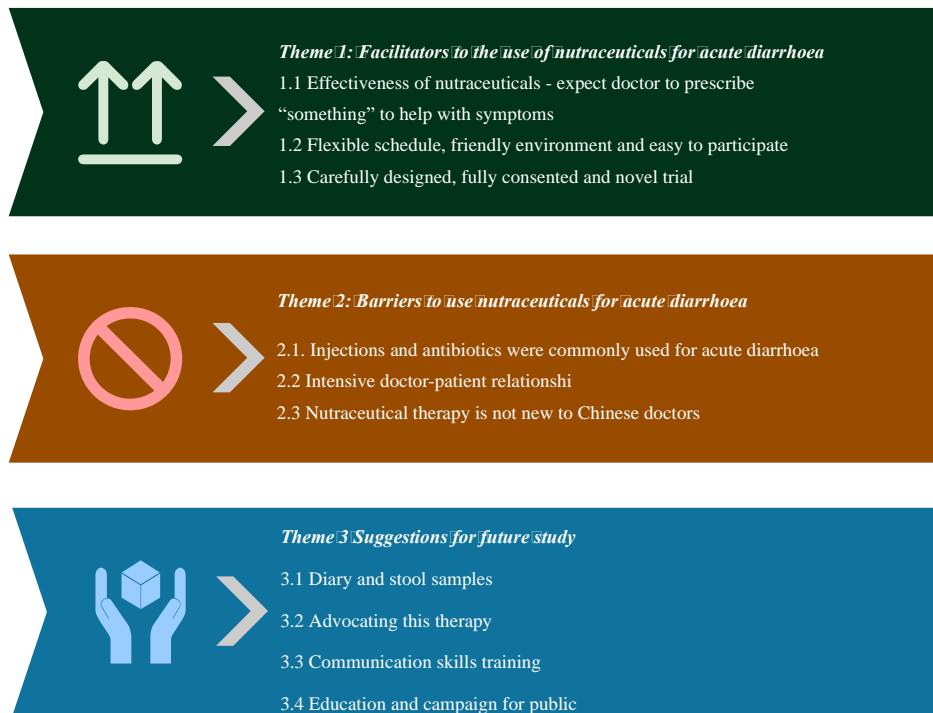
Theme 1: Facilitators to the use of nutraceuticals for acute diarrhoea
1.1 Effectiveness of nutraceuticals - expect doctor to prescribe "something" to help with symptoms
1.2 Flexible schedule, friendly environment and easy to participate
1.3 Carefully designed, fully consented and novel trial

Theme 2: Barriers to use nutraceuticals for acute diarrhoea
2.1. Injections and antibiotics were commonly used for acute diarrhoea
2.2 Intensive doctor-patient relationshi
2.3 Nutraceutical therapy is not new to Chinese doctors

Theme 3 Suggestions for future study
3.1 Diary and stool samples
3.2 Advocating this therapy
3.3 Communication skills training
3.4 Education and campaign for public

Figure 4 Three themes from interviews.

Factors facilitating use of nutraceuticals to manage acute diarrhoea and recruitment included the expectation for doctors to prescribe "something" to relieve symptoms. Both doctors and patients had very positive views on the effectiveness of the nutraceuticals. All interviewed patients and doctors expressed satisfaction with their treatment effects. Some patients even asked what those medications were and where to purchase them. Most interviewed patients felt that this trial had a flexible follow-up schedule and that the research assistants and doctors were friendly and provided very detailed explanations. Most of the doctors and RAs considered this trial was carefully designed and the concept was new.

However, there were also *significant barriers* to use of nutraceuticals to manage acute diarrhoea and to recruitment. Most patients believed antibiotics were "effective" for acute diarrhoea and most doctors would use antibiotics if patients "demand" them, as they worried about patients' satisfaction and subsequent confrontation. All doctors and most RAs mentioned the doctor-patient relationship was a big barrier for trust. There were two arguments during the recruitment period. Half of the doctors would consider antibiotics for acute diarrhoea even without patients' demands as they believed antibiotics are effective and shorten patients' symptom duration. Doctors reported that they were initially suspicious of the anticipated effect as berberine and loperamide were commonly used previously and they did not feel they worked, while curcumin was familiar to them but they had not used it. However, positive patient feedback increased their confidence in this trial. One doctor reported that he started to recruit more patients with higher symptom scores after he observed that patients could accept the therapy and it was seen to be effective. Only two patients complained that turmeric capsules were too big to swallow. As there had not been a randomised trial like this before, doctors agreed that it was hard to tell whether these medicines would really work until they saw the results.

There were *several suggestions* for improving the trial's processes for future studies. Although nine interviewed patients found that the diary was easy to use, four mentioned they could not carefully read and fully understand the diary and one suggested some wording changes. The stool samples were challenging to collect as it was difficult for patients to produce a stool on demand. Communication skills training was suggested by several doctors   for on-site research assistants to allow them to communicate effectively with patients. All research assistants and doctors commented

on the need for public awareness campaigns to reduce the demand for antibiotics and relieve the pressure on doctors. Five patients recommended better provision of information of the adverse effects of unnecessary antibiotic use. Ten patients reported that they wanted the public to benefit as they felt they had a very quick recovery compared with other therapies they used to use. All participants expressed their willingness to recommend this therapy to others and felt this was a meaningful trial and would support using the trial medication.

Table 4 Description of the themes from the interview

Themes	Sub-themes	Example quotes
Theme 1: Facilitators to the use of nutraceuticals for acute diarrhoea	1.1 Effectiveness of nutraceuticals - expect doctor to prescribe "something" to help with symptoms	*"People come to see you and they would always expect you will provide "something" for them. Even if it is placebo, psychologically, they will feel better. It is hard in the Chinese context to not provide any medicines. The patient would feel you are not paying attention to them."* (52 year old male doctor) *"I come to hospital because there is nothing I can do by myself so I would expect the doctors to give me something to help with my symptoms"* (45 year old female patient) *"It was very fast as I only took the medicines twice…then my diarrhoea stopped right away"*. (37 year old male patient) *"could you please tell me what these medicines names are so I can buy (from pharmaceutical stores) by myself next time….."*. (31yo male patient) *"These medicines are effective and most patients are happy with the treatment results"*. (36yo male doctor) There were only two patients who expressed some concerns with side effects (39yo female): *"I am bit worried as I do not know if there are any long term side effects although I asked the doctors and they said it is safe to take…. but I do not know which medicines I am taking…."*. Two patients mentioned the one of the medicines were a too big to swallow. (29yo female) *"I found the yellow medicine was a bit too big to swallow."*
	1.2 Flexible schedule, friendly environment and easy to participate	*"The schedule was very convenient for me as I have to work during the daytime so I can only come to follow up during evening…"*(30yo Female). *"The students (research assistants) are very patient and always answer all the questions in detail, the process was simple and the diary was easy to fill.."* (28yo male).
	1.3 Carefully designed, fully consented and novel trial	*"To be honest, I never saw a trial like this with a really careful design following all standard operating procedures….. especially, you have insurance for the trial…"*. (50 yo male doctor)
Theme 2: Barriers to use nutraceuticals	2.1. Injections and antibiotics were	*"I used to use injections (injectable antibiotics) and it worked very well…"* (49yo female patient)

for acute diarrhoea	commonly used for acute diarrhoea	" if you do not prescribe it (antibiotics) to them, if they get angry, they might chase you with a knife….I do not want to face that….this is very common at the moment, it is hard to be a doctor in China….you might face a life threatening situation as you heard some doctors were killed by patients"(50yo male doctor) . "usually we will give injectable antibiotics if patients insist on 'injection'. " (36 year old male doctor) "I do not know what medicines are inside the injection but I do feel the effect is fast with injections." (36 yo male patient) "In my past experiences, antibiotics are effective, especially for patients who used to use antibiotics, they won't get better until you give them antibiotics as you do not know if they are viral or bacterial infections. Most of the tests are not accurate, so what you can do is to cover bacterial infections in case patients get worse…". (52yo female doctor)
	2.2 Intensive doctor-patient relationship	"One argument was related to trial's recruitment, another was during usual care patients to follow up. Although no one was injured, this indicates the extent of the distrust between doctors and patients. The argument related to trial's recruitment, which resulted in police intervention occurred because a participant's father was suspicious the trial's therapy and came to the hospital to scold the recruiting doctor. They finally went t police office and checked all the documents. Of course they declined the trial after the argument. This is common in China. Although not so many patients are like this, you may occasionally face some patients who seem just to argue with doctors without any reason." (24yo male research assistant) " Currently, the health literacy among the Chinese public is low from what I heard and recently observed from this clinic. They do not have basic knowledge of health….. In China, some of doctors also do not have good knowledge of antibiotics, infection…..and they are used to using them (antibiotics)" . (24yo male research assistant) "it seems to me patients and doctors have had this habit (using injectable antibiotics for acute diarrhoea) for a long time. It is not easy to change a behaviour….. in a short time." (24yo female research assistant)
	2.3 Nutraceutical therapy is not new to Chinese doctors	One doctor (50yo male) mentioned that he started to recruit patients with more prominent symptoms, which he was reluctant to do at the beginning: "I started to recruit patients with higher while blood cell, higher fever, severe belly cramping…".
Theme 3 Suggestions for future study	3.1 Diary and stool samples	There were conflicting reports from patients regarding the use of the diary for symptom report. Nine interviewed patients found that the diary was easy to use. However, four mentioned they could not carefully read and fully understand the diary and one patient suggested some wording changes. "We observed that patients usually do not have stool when they came to hospital as they had diarrhoea symptom at home. In total, we only received a small number of (stool) samples and none were positive for bacterial pathogens. This might need to change in the future study…" (25yo male research assistant).

	3.2 Advocating this therapy for the public	*"I found this is a very meaningful trial and I really hope we will know what those medications are so we can use them in the future or recommend them to families and friends".* (28yo male patient)
	3.3 Communication skills training	*don't say the word 'trial' in Chinese as patients would feel you are treating them like laboratory animals. In reality, not all trials are like that and at least this trial is safe and it is phase 4. Instead saying something like 'research' would be better".* (42yo male doctor) *"we received training from experienced peers who had been trained but we feel it is necessary to have more….".* (23yo male research assistant)
	3.4 Education and campaign for public	*"If patients stop demanding antibiotics or request that antibiotics not be used, this will reverse the situation and consequentially influence doctors' behaviour. It seems easier starting from patients/public rather than with doctors."* (42yo male doctor) *"I usually follow a doctor's advice as I do not know what will be good for me. If someone tells me that acute diarrhoea does not need antibiotics and there are additional side effects from an antibiotic, I won't take it…".* (30yo female patient)

3. Discussion

Summary of findings

Only 21% of patients screened for inclusion into this study were deemed to be eligible, and half of those consented for study enrolment. The follow up was excellent throughout, there was a very low rate of withdrawal and no safety concerns. Both doctors and patients were happy with the treatments and were willing to scale up or recommend to others. Most patients were happy with the diary and considered it easy to use, although some older patients found it more difficult. Blinding was successful.

The main barrier to recruitment is the fraught doctor patient relationship which is common in China. Doctors fear patient dissatisfaction and find it difficult to avoid the deeply entrenched routine of using injections and injectable antibiotics. During consultations many patients requested injections and antibiotics, increasing pressure on doctors to comply, and one patient complaint was only resolved by involving a local policeman.

Although this feasibility study was not powered to detect a difference between groups in the time to recovery, this study does provide support for a larger trial to document the effective use of alternatives to antibiotics for the treatment of acute diarrhoea in China. Only 2% (3/136) of participants used antibiotics, in contrast to the 67% of the patients in routine care at the same hospital during the study period and more than 60% of the prescribed antibiotics were given by injection, although the symptom severity is difficult to compare without a randomly assigned usual care control group. However, all usual care data came from patients diagnosed with acute diarrhoea without co-morbidity within the same age range during the same recruitment period. Some were eligible for inclusion but refused to participate in the trial. A proper designated usual care group will be useful to determine the effective comparison for future scale up.

Comparison with the existing literature

There have been frequent reports of violence and threats of violence against doctors.10   One study identified 459 criminal cases recorded in the Chinese Judgment online system from 2013-2016 involving crimes against healthcare workers in China, 1.6% of cases resulted in death, more than 70%

involved physical abuse.35 In 2019 a new law was passed to protect healthcare workers, which is effective from June 1, 2020.36   Sadly, four days before this law a doctor was killed during an emergency consultation.36 In light of this, most doctors are afraid to take any risks, which might explain why half of the diarrhoea patients were excluded by doctors who considered the patient's condition too serious.

There have been few well-designed studies on traditional Chinese medicines (TCM) as alternatives to antibiotics for relief of symptoms for acute diarrhoea.37,38 Trial insurance requirements were only recently launched in China 39,40 as one of the doctors mentioned that it was the first time he had seen a trial covered by insurance.

This feasibility study has provided evidence that it is possible to implement a trial like this in China in spite of the recruitment challenges observed. Other studies have also shown similar antibiotic use rates in China 41 despite the expansion of antibiotic stewardship in hospitals and the National Action Plan on containing antimicrobial resistance in 2016.42   One national survey on antimicrobial stewardship program (ASP) mentioned that even more than 65% doctors were familiar with ASP only 46% of them had correct answers with ASP test.43 This indicates the urgent need for further training for doctors.

Strengths and Limitations

This is the first feasibility trial investigating the use of nutraceuticals to treat acute diarrhoea in China. A strength of this study is that we used both quantitative and qualitative methods to explore several feasibility challenges. Although the study was under-powered to compare the effectiveness of each nutraceutical, each treatment resulted in symptoms resolving rapidly, and most patients and doctors felt the treatments were effective.

This study has limitations. First, most of the recruited patients experienced very mild symptoms.26 As discussed above, recruitment may have been influenced by the doctors' complex relationship with patients in China.10 Many of the recruited patients were young with a college education level, who might be expected to have lower expectations for antibiotics. We also did not systematically collect stool samples to determine whether bacterial, parasitic or viral infections were present; this was originally planned, but proved logistically difficult in the outpatient setting as patients were mostly unable to provide a stool specimen at the time of consultation.

Implications for policy, practice and further research

Our results suggest that progression to a full randomised trial is feasible. Adequate onsite support will be needed as doctors are very busy and many lack research experience. Minor modifications will be needed to the diary to make it clearer and easier to complete.   The evidence that patients recovered within 48 hours without antibiotics can be used to help doctors and patients accept using alternatives to antibiotics.

From this study we can see that antibiotic stewardship programs are urgently needed in many hospitals and clinics to address over-use of antibiotics especially for those with acute diarrhoea in China. Effective alternatives to antibiotics are likely to be an important intervention for these patients. A large fully powered trial is needed to define the effectiveness by comparing placebo, loperamide, berberine and loperamide + berberine in a wider range of patients with acute diarrhoea in China.

4. Materials and Methods

Setting and participants

Recruitment took place from 10th January to 30th September 2019 in a tertiary care hospital outpatient setting in China, where up to 75% of patients with acute diarrhoea are given antibiotics.25

We recruited adults aged 18 to 70 presenting with acute diarrhoea, defined as at least 3 unformed stools in the previous 24 hours, and with a duration of less than 7 days without complications.26 We

excluded participants with vomiting as the most prominent symptom, visible blood in the stool, temperature greater than 39 degrees, suspected to have acute cholera or pseudomembranous colitis, who were immunocompromised, who had allergy to any of the proposed agents, symptom duration more than 7 days, pregnant women, known chronic bowel disease, established ischaemic heart disease or a history of cardiac arrhythmias, and prolonged QT interval.

Randomisation

The doctors provided participants with a slip with a unique computer-generated random ID number together with a coded intervention group number prepared by the study statistician. After recruitment the participant went to the pharmacist who dispensed the corresponding medication pack. Onsite research assistants (RAs) were available to further answer questions for participants. Recruiting doctors, delivery pharmacists and research assistants were blinded to treatment allocation.

Intervention

Each participant pack contained a 3 day supply of one of the following combinations, and each combination was to be used after each loose stool up to 3 times per day, to stop when the diarrhoea stops:

Group A) loperamide (Xi'an Janssen Pharmaceutical Co.Ltd. 2mg tablets) 4mg initially then 2mg following each loose stool, up to three times per day.

Group B) loperamide used as in A) and berberine (ReYoung Pharmaceutical Co.Ltd.100mg tablets) 100mg up to four times daily following each loose stool.

Group C) loperamide used as in A) and turmeric (contains 6-8% curcumin, Nu U Nutrition, York, UK, 500mg capsules) 500mg up to three times daily following each loose stool.

Group D) the combination of all 3 (loperamide, berberine, and turmeric all as above).

A 'rescue' antibiotic (ciprofloxacin 750mg stat) was given to be used only if symptoms were not starting to settle within 24 hours, after telephone or face-to-face assessment by the designated doctor.

We included non-active nutraceuticals in the medication packs (amino acids) 27 (Zhejiang CONBA Pharmaceutical Co.Ltd.CONBA G20120506 0.8g/tablet) for those individuals not receiving triple therapy so that every individual had three medication containers to use.

All participants were instructed to seek medical assistance again in the event that symptoms progressed. Follow-up was scheduled at 24 hours (telephone, clinic visit if needed), 48 hours (clinic visit), day 7 (clinic visit) and day 14 (telephone).

Outcome measures

Feasibility outcomes included recruitment rate, exclusion rate and reasons, rejection rate and reasons, withdrawal rate and follow-up rate. Each participant was asked to complete a daily symptom diary which has been used successfully in trials of medicines for diarrhoea.24 Exploratory outcomes included use of rescue antibiotics in 24 hours, the duration of symptoms, the proportion with diarrhoea resolved at 24 hours, and the severity of symptoms.

Severity of symptoms

The severity score was documented in the first 48 hours because this is the time when symptoms are the most severe and when nutraceuticals might make an important difference. The diary recorded the number of stools during the previous 24 hours, the consistency of the last stool and the time since the last loose stool. The diary also recorded the severity of symptoms: diarrhoea, vomiting, nausea, abdominal pain, anal burning, fever, disturbed sleep, feeling generally unwell, and interference with normal activities. Each symptom was scored on Likert scales which have been shown to be valid and

sensitive to change for a variety of infections. 28-31 Scores ranged from 0 to 6: 0=no problem, to 6=as bad as it could be. Also documented was the duration of symptoms rated at least moderately bad (3) and the time taken for all symptoms to be rated as very little or no problem (1 or 0).

Statistical analysis

In addition to feasibility outcomes, we aimed to recruit a sufficient sample to detect a difference between 50% using rescue antibiotics in the loperamide group and 15% in any other intervention group (for alpha 0.05 and 80% power), since 50% are likely to have resolved in 24 hours.32,33 We therefore aimed to enrol 30 participants per group with a slight over-enrolment to account for loss to follow up. All analyses were conducted following the intention-to-treat principle. Only complete cases were included, there was no imputation of missing data. Descriptive statistics were used to report feasibility and clinical outcomes, and regression analyses adjusting for number of loose stools at baseline, mean severity and prior duration were conducted for exploratory outcomes where possible. All analyses were performed using STATA 16 (Stata, College Station, TX, USA).

In-depth Interviews

We conducted semi-structured qualitative interviews of patients who participated in this study, and interviewed recruiting doctors and on-site research assistants after trial recruitment was completed. The interviews were conducted by telephone or face to face. Participants were invited to provide verbal consent. We aimed to understand what did and did not work well, whether they were willing to recommend this therapy and suggestions for a future scale up study. Patients and doctors were also asked about what treatment they normally use for acute diarrhoea and whether they would be willing to recommend the trial therapy to others.

5. Conclusions

Recruitment of patients with anything other than mild diarrhoea was very challenging in the current clinical environment in China. Use of loperamide and berberine may relieve symptoms as a viable alternative to antibiotics in China. This approach should be scaled up for further evaluation in a randomised controlled trial to investigate its effectiveness.

List of abbreviations
DIAMOND: Diarrhoea Antibiotic Management using Over-the-counter Nutraceuticals in Daily practice
RCT: Randomised controlled trial
WHO: The world health organization
TCM: Traditional Chinese medicines
OTC: Over-the -counter

Author Contributions: Conception: JYH and PL conceived the study idea, DB conceived the intervention therapy. TF, BS analysed the data. JYH, XDZ and SJW, ZRH, QC contributed to the implementation and data collection. JYH and PL drafted the manuscript. MW, YJH, PL, DB, CG, XZ, MM, revised the protocol and manuscript and all authors had final approval.

Conflicts of Interest:

We declare there are no competing interests.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate: Ethical approval was first obtained by the WHO China Clinical Trials Central Medical Ethics Committee. Reference No: ChiECRCT-2017098. We also obtained the ethical approval from the medical ethics committee of the implementing hospital Shanghai Jiading district centre hospital. Reference No: 201802.

Supplemental table

Supplement table   --Characteristics of interview participants

Interviewee	No	Gender	Age	Education background	Working experiences (Years)
Doctors	1	Male	42	Bachelor	13
	2	Male	36	Bachelor	11
	3	Male	42	Master degree	12
	4	Female	52	Bachelor	28
	5	Male	50	Bachelor	25
					School year
Research Assistants (RAs)	1	Male	24	Master	Year 3
	2	Female	22	PhD	Year 2
	3	Female	24	Master	Year3
	4	Female	25	PhD	Year1
	5	Male	23	Master	Year 3
	6	Female	23	Master	Year1
				Hometown	**Intervention groups**
Patients	1	Male	23	Shanghai	Loperamide & berberine
	2	Male	37	Shanghai	Loperamide & berberine
	3	Female	39	Anhui	Loperamide & turmeric & berberine
	4	Female	29	Shanghai	Loperamide & turmeric
	5	Female	49	Shanghai	Loperamide & turmeric & berberine
	6	Female	30	Jiangxi	Loperamide & turmeric & berberine
	7	Male	40	Shangdong	Loperamide only
	8	Male	22	Helongjiang	Loperamide only
	9	Female	45	Shanghai	Loperamide & turmeric
	10	Female	34	Shanghai	Loperamide & berberine
	11	Female	32	Shanghai	Loperamide & turmeric
	12	Male	28	Fujian	Loperamide & turmeric & berberine
	13	Male	31	Shanghai	Loperamide only
	14	Male	36	Hunan	Loperamide & berberine

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