BMJ Open

Optimising the treatment for uncomplicated acute appendicitis (OPTIMA trial): a protocol for a multicentre, randomised, double-blinded placebo-controlled study

Jie Wu,[1] Haiyang Jiang,[1] Shikuan Li,[2] Xiuwen Wu,[3] Peige Wang ![ORCID],[2] Robert Sawyer,[4] Jianan Ren ![ORCID] [3]

For numbered affiliations see end of article.

Correspondence to
Professor Jianan Ren;
jiananr@gmail.com,
Dr Robert Sawyer;
robert.sawyer@med.wmich.edu and
Dr Peige Wang;
wpgzyz@163.com

ABSTRACT

Introduction Emerging evidence has shown that an antibiotic first strategy is a viable treatment option for uncomplicated acute appendicitis (AA). Although there has recently been an interest and increase in the use of antibiotics as the primary strategy for treating uncomplicated AA, there is no consensus regarding the optimum antibiotic regimen. In particular, the long-term outcomes of different antibiotic regimens, such as the recurrence rate, still lack evidence. Given that the flora of the appendix is mainly anaerobic bacteria, we hypothesised that antianaerobe regimens could decrease the recurrence rate compared with those that did not include antianaerobic antibiotics.

Methods and analysis The OPTIMA(Optimising the treatment for uncomplicated acute appendicitis) trial is a multicentre, double-blinded placebo-controlled superiority randomised study aimed to evaluate the role of antianaerobic antibiotics in the resolution of uncomplicated AA. Patients (18–65 years) with uncomplicated AA (without gangrenous, perforated appendicitis, appendiceal abscess, or appendiceal fecaliths) are eligible for inclusion. The primary endpoint of this study is the success rate of the treatment, defined as the resolution of AA resulting in discharge from the hospital without surgical intervention and recurrent symptoms within one year. Secondary endpoints include mortality, postintervention complications, recurrent symptoms up to one year after treatment, hospital stay, sick leave, treatment cost, pain symptom scores and quality of life. Data are reported as the number of cases (%), median (range) and relative risk, which will be analysed using the Mann-Whitney U test or χ^2 test, as appropriate. P-value<0.05 will be considered significant.

Ethics and dissemination The protocol has been approved by the Ethics Committee of Jinling Hospital on 13 November 2018 (2018NZKY-027-01). The trial findings will be published in peer-reviewed journals.

Trial registration number ChiCTR1800018896.

Strengths and limitations of this study

► The OPTIMA(Optimising the treatment for uncomplicated acute appendicitis) trial is the first multicentre, randomised, double-blinded placebo-controlled clinical study comparing ceftazidime combined with ornidazole versus ceftazidime combined with placebo for uncomplicated acute appendicitis to investigate the role of antianaerobic drugs in the conservative treatment of appendicitis.

► A double-blinded trial with a placebo can reduce bias and confirm the role of antianaerobic agents in the treatment of appendicitis.

► The data will be collected and saved in an electronic data capture system to guarantee the integrity of the data. The data engineers will organise and check the data from each centre to reduce errors in the data collection process.

► Since the treatment of uncomplicated appendicitis in the precent study involves antibiotics alone, we cannot collect data on surgical pathology and bacteriological analysis, unless surgical intervention is required.

17.7 million cases (incidence, 228/100 000).[2] Appendectomy was first proposed by McBurney in 1894.[3] For more than a century since then, appendectomy has been the gold standard treatment for appendicitis and has been widely applied in clinical practice. However, the treatment of AA has been under active debate and discourse in recent years. The increasing amount of evidence has shown that most patients with uncomplicated AA can be treated with antibiotics alone instead of surgery.[4–12] Therefore, the guidelines recommend antibiotic treatment for uncomplicated AA when patients accept the recurrence risk.[13]

At present, there is no consensus on the choice of antibiotics, and various antibiotic regimens have been adopted. Some recent clinical

INTRODUCTION

Acute appendicitis (AA) is one of the most common indications for emergency surgery worldwide.[1] In 2019, there were an estimated

studies have focused on defining a better regimen, including the route of administration, course of treatment, and even supportive care without antibiotics.[5 14–19] A randomised clinical trial on antibiotic therapy for uncomplicated AA from Finland showed that antibiotic therapy is non-inferior to appendectomy, in which antibiotic therapy was intravenous ertapenem for 3 days followed by 7 days of oral levofloxacin combined with metronidazole.[15] Park *et al* performed a single-blinded (participants only) trial and reported results regarding the possible spontaneous resolution of uncomplicated AA.[16] The APPAC (Appendicitis Acuta) group recently designed and published a protocol for a multicentre, double-blinded placebo-controlled superiority randomised study comparing antibiotic therapy with placebo for the treatment of CT scan-confirmed uncomplicated AA to evaluate the role of antibiotics in the resolution of uncomplicated AA (NCT03234296).

However, the antibiotics used in these trials are not the preferred choice in most countries, including China. According to our previous study, three generations of intravenously administered cephalosporins with or without nitroimidazoles are the most common regimens, and the usage of antimicrobial drug regimens in conservative treatment for AA lacks standardisation and rationale.[20] Additionally, antibiotic regimens in clinical trials or guidelines also vary, which can confuse physicians regarding the choice of conservative AA treatment.

The trial from Park *et al* showed a higher tendency of recurrence of appendicitis in the no-antibiotic group than in the antibiotic group. Considering Park *et al*'s study was not a double-blinded and multicentre study, it is necessary to conduct larger sample size trials to prove the correctness of the conclusion.[16] In addition, cephalosporins combined with nitroimidazoles as preoperative prophylactic antibiotic regimens have been proven to reduce the incidence of surgical site infection (SSI) compared with cephalosporins alone in both patients with uncomplicated and complicated AA.[21] A prospective double-blinded randomised controlled trial revealed a significant decrease in wound infection rates with two postoperative intravenous doses of antibiotics, suggesting that postoperative antibiotics are of benefit in uncomplicated appendicitis.[22] Some etiological studies also suggested that anaerobic bacteria are an indispensable risk factor for uncomplicated appendicitis progression.[23–26] Accordingly, we hypothesised that a combination of antianaerobe drug regimens would have stronger effects on decreasing the recurrence of AA.

To our knowledge, this double-blinded randomised controlled study is the first to evaluate the therapeutic efficiency (a composite primary outcome including in-hospital cure rate, transfer rate and recurrence rate within a one-year follow-up period) of the antianaerobe covered strategy compared with antianaerobic uncovered regimens in uncomplicated AA, providing a reference for rational antibiotic selection.
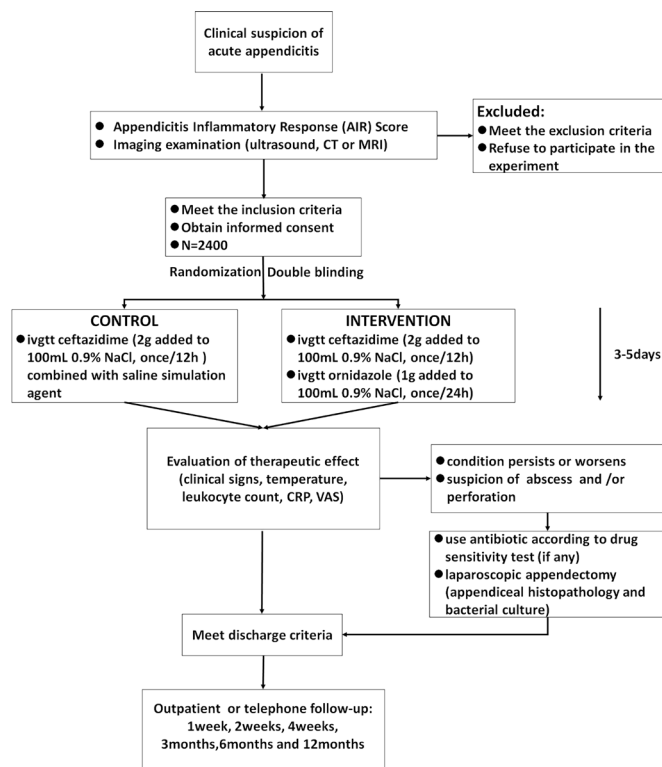

Figure 1 OPTIMA(Optimising the treatment for uncomplicated acute appendicitis) flow chart of enrolment, interventions and follow-up. CRP, C-reactive protein; ivgtt, intravenous drip; VAS, visual analogue scale.

METHODS
Trial design
The OPTIMA(Optimising the treatment for uncomplicated acute appendicitis) trial is a multicentre, randomised, double-blinded parallel-controlled clinical trial designed to evaluate the therapeutic qualities and efficiency of the combination of antianaerobe strategies compared without use of antianaerobic agents. At each centre, patients are randomly allocated to the experimental treatment arm (intravenously administered ceftazidime combined with ornidazole) or the control arm (intravenously administered ceftazidime combined with a saline simulation agent) in a 1:1 ratio. Figure 1 shows the enrolment process, interventions and follow-up of two groups.

Trial setting
The trial will take place at 80 hospitals in China. All participating hospitals will recruit a specified number of patients according to the annual admission volume of each centre. At all participating hospitals, appendectomy is usually performed laparoscopically.

Diagnosis
A rapid and correct diagnosis of uncomplicated appendicitis is the key to the success of the study. First, imaging has irreplaceable advantages in diagnosing and differentiating uncomplicated appendicitis. Moreover, due to the high sensitivity and specificity of the appendicitis

inflammatory response (AIR) score in the identification of advanced appendicitis, we combined the AIR score and imaging tests to diagnose uncomplicated appendicitis.[27–32] All patients with clinically suspected AA will be enrolled for further screening. Clinical history, physical examination, and laboratory tests, including routine blood tests (white cell count, proportion of polymorphonuclear leucocytes), C-reactive protein, creatinine and female human chorionic gonadotropin, will be evaluated by the surgeon. The AIR score will be recorded according to the inspection results to define three groups: low probability (<5 points), medium probability (5–8 points) and high probability (>8 points). Then, all patients will undergo imaging.

Inclusion criteria
▶ Ages 18–65 years.
▶ AIR score: low probability (<5 points), medium probability (5–8 points).
▶ Diagnosis of uncomplicated AA confirmed by imaging (ultrasound, CT, or MRI) defined by the following criteria: appendix diameter greater than 6 mm, thickened appendix wall, appendix lumen stenosis, inflammatory oedema and a small amount of effusion around the appendix.

Exclusion criteria
▶ Age <18 or >65.
▶ AIR score >8.
▶ Diagnosis of existing complications by imaging (ultrasound, CT, or MRI), such as abscess, appendiceal fecalith or perforation.
▶ Appendiceal tumour with or without appendiceal soft tissue mass.
▶ History of acute or chronic appendicitis.
▶ Suspicion of severe sepsis.
▶ Patients with a known history of allergies or other contraindications to the study of antibiotics.
▶ Immunocompromised patients.
▶ Patients undergoing other antibiotic treatments.
▶ Alcoholics.
▶ Women who are pregnant or plan to become pregnant or who are breast feeding within three months of the study.
▶ Refusal to sign the informed consent.

Allocation and randomisation
Due to differences in the volume of visits from each hospital, the data analyst will assign a fixed number of cases to each subcentre based on its annual volume. SAS V.9.1 software will be used to achieve stratified block randomisation. The researchers will be blinded to the stratified randomisation process and the results of patient randomisation. The patients meeting the trial criteria will be randomly assigned to arm A (ceftazidime combined with placebo group) or arm B (ceftazidime combined with ornidazole group) in a 1:1 ratio after signing the informed consent. Each patient will be given

a unique study number, undergo random grouping and be assigned a designated treatment with 'Jinling Rat' random allocation software. The pharmacists will obtain treatment packages in similar containers that are distinguishable only by a patient's unique identification number. To ensure patient safety in an emergency, data analysts will provide each hospital with an emergency unblinding list that includes the specific drugs used by the patients participating in the trial. Each hospital should use it only in critical situations, such as when a patient has severe allergies to the treatment drug in the study.

Blinding
Jinling Rat software is a random allocation tool used to maintain double-blinding throughout the whole process of the trial. The investigators and the patients remain unaware of the treatment packages until the study is finished and the data have been locked.

Follow-up will be conducted by the surgeon at each centre either by telephone or outpatient visits. The surgeon who performs the follow-up is unaware of the patient's previous antibiotic regimen and records only the required information on the follow-up form.

Sample size calculation
Given the results of previous studies indicating that antibiotics have a success rate of approximately 75% in treating uncomplicated appendicitis, the recurrence rate within 1 year is 25%–35%. The recurrence rate with antibiotic treatment for appendicitis is highest within the 3 months after discharge.[7 9 15 16] We estimate that the success rate of the combination of antianaerobic drugs can increase the cure rate from 75% to 80%. Under this condition, we calculated that a minimum of 1091 patients in each group would achieve a power of 0.8 (1-β) and a one-sided significance level (α) of 0.025 to conclude that the efficacy of the intervention arm is superior to that of the control arm regarding the long-term cure rate.

In addition, some relevant studies have chosen short-term efficacy as the primary outcome considering that AA is an acute phase disease and that antibiotics will not affect subjects after drug metabolism. Therefore, those studies have selected the response rate after a course of drug therapy as the primary outcome. Under this condition, we projected the sample size of 564 participants for each group with 90% power at a two-sided alpha level of 0.05 using PASS software (PASS V.11, NCSS software, Kaysville, USA) to conclude that the efficacy of the intervention arm is superior to that of the control arm (from 96% to 99%).

Therefore, to sufficiently analyse both the short-term and long-term efficacy of antibiotic therapy, we chose the first algorithm for sample size estimation, and a total of 2400 patients will be recruited, given an estimated dropout rate of 10% of all patients.

Recruitment plan

Recruitment of participants will start in January 2022, and follow-ups should be carried out at the same time. All 2400 patients are expected to be enrolled by the end of 2022.

Interventions
Antibiotic use protocol

Patients will be randomly assigned in a 1:1 ratio to either the experimental treatment arm (intravenously administered ceftazidime combined with ornidazole) or the control arm (intravenously administered ceftazidime combined with an ornidazole simulation agent). The experimental treatment group will receive ceftazidime (2 g added to 100 mL 0.9% NaCl injection for intravenous drip, once every 12 hours)+ornidazole (1 g added to 100 mL 0.9% NaCl injection for intravenous drip, once every 24 hours) for 3–5 days of routine treatment. The control group will receive ceftazidime (2 g added to 100 mL 0.9% NaCl injection for intravenous drip, once every 12 hours)+simulation agent (two doses added to 100 mL 0.9% NaCl injection for intravenous drip, once every 12 hours) for 3–5 days of routine treatment. In both groups, the maximum extension will not be more than 7 days, depending on the treatment response.

Criteria for transferring to another treatment

In the case of a confirmed source of infection through the drug sensitivity test, appropriate antimicrobial agents can be adopted. If conservative treatment for 24 hours is not effective or the patient's condition worsens, the treatment strategies should be switched immediately. When an exacerbation of the infection or the occurrence of perforated appendicitis or diffuse peritonitis is suspected, patients will undergo an emergency laparoscopic appendectomy and appendiceal histopathology and bacterial culture.

Discharge and follow-up

Patients meeting the clinical cure criteria will be discharged, which means that the following criteria must be met at the same time: body temperature (underarm) <37.5°C, white cell count <10.0×10^9/L, neutrophil percentage <70% and no deep tenderness, mass or rebound pain in the right lower abdomen of the subjects during follow-up after treatment with the medication. According to the duration of conservative treatment, the hospitalisation follow-up time will be set to 1 week. The following indicators will be collected on days 1, 3, 5 and 7: a physical examination, including the visual analogue scale (VAS), auxiliary examination, therapeutic effect and surgery status (if any). An outpatient follow-up visit is recommended 1 week after discharge. Standard follow-ups of 2 weeks, 1 month, 3 months, 6 months and 1 year will be performed by the surgeon either by telephone or in an outpatient setting. For patients treated surgically, follow-up should include the assessment of SSI in 1 month.

If the patient is treated conservatively or surgically for recurrent appendicitis after discharge, the time and components of treatment should be recorded.

Preparation before implementation

Before the commencement of the clinical trial, the investigators will be trained on the trial protocol by the head of each trial centre. Each investigator should understand the content of this clinical trial protocol and master the standard methods of enrolment, recording and judgement criteria according to standard operating procedure and Good Clinical Practice guidelines. All participating surgeons and residents should accept standard training on the unified assessment methods for classifying different types of AA.

Outcome measures
Primary outcome measure

The primary endpoint of this study is evaluation of the efficiency and long-term outcome of ceftazidime combined with ornidazole compared with ceftazidime combined with placebo. It is hypothesised that ceftazidime combined with ornidazole is superior to ceftazidime combined with placebo and will increase the 1-year cure rate. The efficiency of non-operative management (NOM) of uncomplicated appendicitis will be measured on many aspects, including the initial cure rate, need for operation and long-term recurrence rate.

The definition of recurrence is based on clinical, imaging and/or histopathological diagnosis during follow-up. When subjects experience relevant symptoms and signs, further laboratory inspection and imaging diagnosis of AA will be required. All patients with recurrent appendicitis will undergo a laparoscopic appendectomy. Histopathological diagnosis results and bacterial culture results during surgery will be recorded to identify recurrence.

Secondary outcome measures

Secondary endpoints are the evaluation of the total length of hospital stay, total expenses during hospitalisation, mortality, duration of antibiotic treatment, complication rate, time to fulfil discharge criteria, pain score (VAS), the use of analgesics, quality of life assessment (12-Item Short Form Health Survey), readmission rate, percentage of patients requiring appendectomy during initial antibiotic therapy and the number of days absent from work. Complications will be classified according to conservative treatment, such as antibiotic-related adverse reactions, or surgery, such as the incidence of SSI, incisional hernia, anastomotic fistula, abdominal abscess and adhesions. The details of the data collection are shown in figure 2.

Management and analysis of data
Data collection and management

The data managers of the statistical unit are responsible for the data management. At each subcentre, the complete raw information of patients will be stored in electronic medical records and paper medical records to facilitate

		Hospitalization				*Follow-up after discharge					
Timepoint	1day	3days	5days	7days	Discharge	1week	2weeks	4weeks	3months	6months	12months
Personal Data											
Demographic information	√										
Previous medical history	√										
Allergic history	√										
Inspection Items											
Physical examination	●——————————————————————●										
VAS score	●——————————————————————●										
**Imaging examination	●————————●										
***Blood indexes	●————————●										
**Bacterial culture and drug sensitivity results	●————————●										
***Prognosis											
Complication	●——————————————————————●										
Adverse reactions	●——————————————————————●										
Surgical records	●——————————————————————●										
Efficacy evaluation											
Compliance	●——————●										
Hospital stay					√						
Medical expenses					●—————————————————————●						
Quality of life assessment						●———————————————————●					

Figure 2 Follow-up schedule of OPTIMA(Optimising the treatment for uncomplicated acute appendicitis). *Follow-up after discharge can be conducted either by telephone or in an outpatient clinic as recommended. **If symptoms of suspected appendicitis appear during follow-up after discharge, relevant examinations should be performed and records should be made. ***Patients undergoing surgical treatment should be recorded separately including disease complications and surgical complications as well as their respective adverse events. VAS, visual analogue scale.

later review. Baseline demographics, as well as the relevant variables of antibiotic treatment and surgery, will be recorded independently by two data administrators. All variables that need to be counted are provided in the full study protocol. These variables should be registered in case report forms (CRFs), which will be entered into ResMan, an electronic data collection and management system supported by the Chinese Clinical Trial Registry. Data will be encrypted and can be processed only with the authorisation of the data managers. A detailed response questionnaire will be used by the data managers to record missing and incorrect data. Then, the investigator will verify the raw materials kept by the hospital.

Statistical analysis

The analysis of primary measures will be based on the intention-to-treat (ITT) set, and secondary outcomes will be analysed with the per-protocol (PP) set. The safety analysis will be performed on the safety set. When ITT is used for analysis, missing results will be filled by statistical models based on their data distribution type. The sets are defined as follows:

► ITT set: this set consists of all randomised subjects who have used the study drug at least once and have at least one postdrug efficacy evaluation.
► PP set: this set includes all randomised subjects who complete all follow-ups as required by the protocol, have no major protocol violations and have good compliance (medication compliance between 80% and 120%).

► Safety set: this set refers to all the subjects who entered the study, used the study drug at least once and were evaluated for safety after using the medication.

All statistical analyses will be performed with SAS V.9.1 system programming. All statistical tests, except for the superiority test (a one-sided test) of the primary measures, will be conducted on a bilateral basis. Continuous variables are described as the mean and SD or median and upper and lower quartiles. Categorical variables are described as frequency and proportion. The one-sided 97.5% CI for proportion difference will be calculated to evaluate the treatment difference (one-sided test at $\alpha=0.025$). The secondary outcomes will be analysed using different statistical methods according to the types of data. The t-test or Wilcoxon rank-sum test is usually used to compare continuous variables between two groups, and the χ^2 test or Fisher's exact probability test is usually used to compare categorical variables. P-values less than 0.05 indicates statistical significance for all secondary outcome analyses.

Safety and data monitoring

The statisticians in charge of randomisation are responsible for unblinding information when subjects need to know the specific drugs used in case of emergency. In the case of adverse events, the observing physician can decide whether to terminate the observation based on the condition of the disease.

Regular on-site monitoring visits to the trial hospital will be conducted by designated personnel to ensure that all aspects of the clinical trial protocol are strictly followed and that the source data will be verified to ensure conformance with the CRFs. At the same time, the principal investigators and the heads of statistical analysis units will form a data management review committee (DMRC). Before the end of the follow-up and data locking, meetings must be held to individually review questionable data and/or the relationship between adverse events and drugs.

ETHICS AND DISSEMINATION
Ethics

The protocol has been approved by the Ethics Committee of Jinling Hospital on 13 November 2018 (2018NZKY-027-01). This trial will be conducted following the Helsinki Declaration and the relevant Chinese clinical trial research norms and regulations.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, reporting, dissemination plans of our research.

Protection of the rights and interests of patients

Before starting this trial, research physicians should inform patients of the trial details in writing, including the nature of the clinical trial, the purpose of the trial, the expected benefits, and the risks. The researchers are

responsible for protecting the privacy of the participating patients. Even if the patients decide to withdraw from the trial at any stage, their medical benefits and rights will not be affected, and they can continue receiving other effective treatment. For possible adverse events, the experiment will also design corresponding solutions. In addition, after the investigation is completed, the patients will be given the results by telephone. Translated written consent is attached as an online supplemental file.

Dissemination plan

The trial findings will be published in peer-reviewed journals and will also be disseminated through presentations at national and/or international conferences.

DISCUSSION

The optimisation of NOM of appendicitis, including the dosage form and duration of antibiotic use, is being actively researched.[15] However, the types of antibiotics used in studies vary, and the selected antibiotics are not common in many regions worldwide, such as low-level and middle-level developing countries. In addition, the role of antianaerobic agents in the treatment of uncomplicated appendicitis remains to be explored and emphasised. These factors make it difficult for clinicians to choose a reasonable antibiotic regimen for appendicitis.

Some studies showed that only supportive care of uncomplicated AA or diverticulitis is non-inferior to antibiotics.[16 33 34] However, many etiological studies have demonstrated that anaerobic bacteria especially *Fusobacterium nucleatum/necrophorum* are an independent risk factor for AA.[23–26] There is currently a lack of a multicentre randomised controlled trial exploring the necessity of antianaerobic agents in the NOM of uncomplicated appendicitis.

According to our previous retrospective study, cephalosporin alone and cephalosporin combined with nitroimidazole are common clinical treatment protocols and have similar short-term outcomes in the treatment of uncomplicated AA in China. However, few studies have compared the long-term outcomes of the different treatment strategies due to the lack of follow-up information after discharge.[20] To our knowledge, to date, no doubleblinded randomised controlled trials have compared three generations of cephalosporins combined with ornidazole in the treatment of uncomplicated AA. Thus, we designed the OPTIMA trial to evaluate the safety and efficacy of a combination of antianaerobic agents in the treatment of uncomplicated AA and its prognostic impact. The results of this study are of great significance for guiding clinical antibiotic use in an environment where antibiotic treatment regimens are not standardised and rational.

Strengths and limitations of this study

In this trial, ultrasound, CT, and MRI are both chosen as examination techniques for appendicitis, since the accurate distinction between complicated and uncomplicated

AA is the key to rational treatment of appendicitis. Considering that CT is not available at night at several non-teaching hospitals, patients with milder conditions may be reluctant to undergo more expensive CT and MRI scans. If we exclude these patients, it might increase the selection bias of the trial due to economic and time factors. The overall sensitivity and specificity are 76% and 95% for ultrasound and 99% and 84% for CT, respectively, and MRI is at least as sensitive and specific as CT.[35–37] Moreover, recent studies have shown that the AIR score has an advantage in diagnosing appendicitis due to its high sensitivity and specificity.[27–32] Therefore, a combination of the AIR score and imaging will be used to diagnose uncomplicated appendicitis in this study. All examination items and results will be stored in a timely manner in the ResMan system, the data will be verified and re-evaluated at any time by the dedicated DMRC and patients who do not meet the criteria for uncomplicated appendicitis will be excluded. Thus, the diagnosis of uncomplicated AA in this trial is reliable.

In terms of antibiotic selection, ertapenem is a broadspectrum antibiotic with an antianaerobic effect that has been shown to be effective in treating appendicitis in previous studies and is recommended in the guidelines.[13] However, compared with ertapenem, which is expensive and difficult to obtain, the antibiotics chosen in this study are readily available and safe, making the experimental results easier to popularise. In addition, according to previous studies, antibiotic treatment for uncomplicated AA was shown to have the highest recurrence rate during the first 3 months after discharge.[6 7 9] We speculate that this finding is related to anaerobic bacteria in the intestinal tract. Thus, we plan to test this by comparing ceftazidime plus placebo with ceftazidime plus ornidazole for uncomplicated AA because of the excellent antianaerobic activity of nitroimidazoles.[38–40]

To date, this study has the largest sample size among uncomplicated AA studies to evaluate the short-term and long-term prognoses. This study discusses the efficacy of combined antianaerobic drugs in the treatment of uncomplicated appendicitis and focuses on the cure rate and recurrence rate of patients during the follow-up period after discharge and explores methods for reducing the recurrence rate of appendicitis.

For uncomplicated AA, it is difficult to obtain bacteriological evidence from the patient's abdominal cavity. In this study, bacteriological data are collected only when patients require surgical treatment. Therefore, the antianaerobic drugs were selected based on a 2016 study of clinical characteristics and antimicrobial patterns in complicated intra-abdominal infections in China.[41] In addition, a 2017 retrospective study of appendicitis treatment reached similar conclusions about antibiotic use.[20] There were other limitations to this study. We did not set a placebo group with only supportive care considering the safety and interests of patients. However, it is feasible to explore the role of antianaerobic agents in uncomplicated appendicitis. Moreover, a sufficiently large sample

and 1 year of standardised follow-up are required to investigate the effect of antianaerobic drugs on the long-term outcome of appendicitis. This is a challenge for the subcentres in how to conduct research operations in an emergency department setting and how to respond promptly and accurately to emergency problems.

Author affiliations
[1]Department of General Surgery, The Affiliated BenQ Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, China
[2]Department of Emergency Medicine, The Affiliated Hospital of Qingdao University, Qingdao, China
[3]Department of Surgery, Jinling Hospital, Nanjing Medical University, Nanjing, Jiangsu, China
[4]General Surgery Department, Western Michigan University, Kalamazoo, Michigan, USA

Contributors All authors were involved in the study design, and read and approved the final manuscript. JR, RS and PW contributed to conception and design of this study. JW and HJ provided statistical advice. JW, HJ, SL and XW are responsible for contacting with the subcentres. JR, RS, PW, XW and JW are members of data management review committee. JW and HJ drafted the manuscript.

Competing interests Jingdong Junzhuo Pharmaceutical provides the study drugs (ornidazole and sodium chloride injection, ceftazidime injection and simulants) for this investigator-initiated study but has no influence on the study design, data analysis or report. The investigators take full responsibility for the integrity and content of this paper.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs
Peige Wang http://orcid.org/0000-0002-4890-9964
Jianan Ren http://orcid.org/0000-0002-4697-4762

REFERENCES

1 Stewart B, Khanduri P, McCord C, *et al*. Global disease burden of conditions requiring emergency surgery. *Br J Surg* 2014;101:e9–22.
2 Wickramasinghe DP, Xavier C, Samarasekera DN. The worldwide epidemiology of acute appendicitis: an analysis of the global health data exchange dataset. *World J Surg* 2021;45:1999–2008.
3 McBurney C. IV. The incision made in the abdominal wall in cases of appendicitis, with a description of a new method of operating. *Ann Surg* 1894;20:38–43.
4 CODA Collaborative, Flum DR, Davidson GH, *et al*. A randomized trial comparing antibiotics with appendectomy for appendicitis. *N Engl J Med* 2020;383:1907–19.
5 Georgiou R, Eaton S, Stanton MP, *et al*. Efficacy and safety of Nonoperative treatment for acute appendicitis: a meta-analysis. *Pediatrics* 2017;139:e20163003.
6 Huang L, Yin Y, Yang L, *et al*. Comparison of antibiotic therapy and appendectomy for acute uncomplicated appendicitis in children: a meta-analysis. *JAMA Pediatr* 2017;171:426–34.
7 Salminen P, Paajanen H, Rautio T, *et al*. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. *JAMA* 2015;313:2340–8.
8 Salminen P, Tuominen R, Paajanen H, *et al*. Five-Year follow-up of antibiotic therapy for uncomplicated acute appendicitis in the APPAC randomized clinical trial. *JAMA* 2018;320:1259–65.
9 Vons C, Barry C, Maitre S, *et al*. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. *Lancet* 2011;377:1573–9.
10 Andersson RE. The role of antibiotic therapy in the management of acute appendicitis. *Curr Infect Dis Rep* 2013;15:10–13.
11 Andersson RE, Petzold MG. Nonsurgical treatment of appendiceal abscess or phlegmon: a systematic review and meta-analysis. *Ann Surg* 2007;246:741–8.
12 Park H-C, Kim MJ, Lee BH. The outcome of antibiotic therapy for uncomplicated appendicitis with diameters ≤ 10 mm. *Int J Surg* 2014;12:897–900.
13 Di Saverio S, Podda M, De Simone B, *et al*. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. *World J Emerg Surg* 2020;15:27.
14 Wang Q, Morikawa Y, Ueno R, *et al*. Prognosis of ultrasonographic low-grade pediatric appendicitis treated with supportive care. *Surgery* 2021;170:215–21.
15 Sippola S, Haijanen J, Grönroos J, *et al*. Effect of oral moxifloxacin vs intravenous ertapenem plus oral levofloxacin for treatment of uncomplicated acute appendicitis: the APPAC II randomized clinical trial. *JAMA* 2021;325:353–62.
16 Park HC, Kim MJ, Lee BH. Randomized clinical trial of antibiotic therapy for uncomplicated appendicitis. *Br J Surg* 2017;104:1785–90.
17 Köhler F, Acar L, van den Berg A, *et al*. Impact of the COVID-19 pandemic on appendicitis treatment in Germany-a population-based analysis. *Langenbecks Arch Surg* 2021;406:377–83.
18 Neufeld MY, Bauerle W, Eriksson E, *et al*. Where did the patients go? changes in acute appendicitis presentation and severity of illness during the coronavirus disease 2019 pandemic: a retrospective cohort study. *Surgery* 2021;169:808–15.
19 Talan DA, Saltzman DJ, Mower WR, *et al*. Antibiotics-First Versus Surgery for Appendicitis: A US Pilot Randomized Controlled Trial Allowing Outpatient Antibiotic Management. *Ann Emerg Med* 2017;70:1–11.
20 Wu J, Li M, Liu Q, *et al*. Current practice of acute appendicitis diagnosis and management in China (PANDA-C): a national cross-sectional survey. *Surg Infect* 2021;22:973–82.
21 Zhang X, Wang Z, Chen J, *et al*. Incidence and risk factors of surgical site infection following colorectal surgery in China: a national cross-sectional study. *BMC Infect Dis* 2020;20:837.
22 Mennie N, Panabokke G, Chang A, *et al*. Are postoperative intravenous antibiotics indicated after laparoscopic appendicectomy for simple appendicitis? A prospective double-blinded randomized controlled trial. *Ann Surg* 2020;272:248–52.
23 Hattori T, Yuasa N, Ikegami S, *et al*. Culture-Based bacterial evaluation of the appendix lumen in patients with and without acute appendicitis. *J Infect Chemother* 2019;25:708–13.
24 Rautio M, Saxén H, Siitonen A, *et al*. Bacteriology of histopathologically defined appendicitis in children. *Pediatr Infect Dis J* 2000;19:1078–83.
25 Rogers MB, Brower-Sinning R, Firek B, *et al*. Acute appendicitis in children is associated with a local expansion of fusobacteria. *Clin Infect Dis* 2016;63:71–8.
26 Swidsinski A, Dörffel Y, Loening-Baucke V, *et al*. Acute appendicitis is characterised by local invasion with Fusobacterium nucleatum/ necrophorum. *Gut* 2011;60:34–40.
27 Andersson M, Kolodziej B, Andersson RE. Validation of the appendicitis inflammatory response (air) score. *World J Surg* 2021;45:2081–91.
28 Kularatna M, Lauti M, Haran C, *et al*. Clinical prediction rules for appendicitis in adults: which is best? *World J Surg* 2017;41:1769–81.
29 Kollár D, McCartan DP, Bourke M, *et al*. Predicting acute appendicitis? A comparison of the Alvarado score, the appendicitis

inflammatory response score and clinical assessment. *World J Surg* 2015;39:104–9.

30 de Castro SMM, Ünlü C, Steller EP, *et al*. Evaluation of the appendicitis inflammatory response score for patients with acute appendicitis. *World J Surg* 2012;36:1540–5.

31 Yeşiltaş M, Karakaş Dursun Özgür, Gökçek B, *et al*. Can Alvarado and appendicitis inflammatory response scores evaluate the severity of acute appendicitis? *Ulus Travma Acil Cerrahi Derg* 2018;24:557–62.

32 Andersson M, Andersson RE. The appendicitis inflammatory response score: a tool for the diagnosis of acute appendicitis that outperforms the Alvarado score. *World J Surg* 2008;32:1843–9.

33 Chabok A, Påhlman L, Hjern F, *et al*. Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. *Br J Surg* 2012;99:532–9.

34 Daniels L, Ünlü Ç, de Korte N, *et al*. Randomized clinical trial of observational versus antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis. *Br J Surg* 2017;104:52–61.

35 Eng KA, Abadeh A, Ligocki C, *et al*. Acute appendicitis: a meta-analysis of the diagnostic accuracy of US, CT, and MRI as second-line imaging tests after an initial us. *Radiology* 2018;288:717–27.

36 Kim MS, Kwon H-J, Kang KA, *et al*. Diagnostic performance and useful findings of ultrasound re-evaluation for patients with equivocal CT features of acute appendicitis. *Br J Radiol* 2018;91:20170529.

37 Kave M, Parooie F, Salarzaei M. Pregnancy and appendicitis: a systematic review and meta-analysis on the clinical use of MRI in diagnosis of appendicitis in pregnant women. *World J Emerg Surg* 2019;14:37.

38 Nord CE. In vitro activity of quinolones and other antimicrobial agents against anaerobic bacteria. *Clin Infect Dis* 1996;23 Suppl 1:S15–18.

39 Löfmark S, Edlund C, Nord CE. Metronidazole is still the drug of choice for treatment of anaerobic infections. *Clin Infect Dis* 2010;50 Suppl 1:S16–23.

40 Freeman CD, Klutman NE, Lamp KC. Metronidazole. A therapeutic review and update. *Drugs* 1997;54:679–708.

41 Ouyang W, Xue H, Chen Y, *et al*. Clinical characteristics and antimicrobial patterns in complicated intra-abdominal infections: a 6-year epidemiological study in southern China. *Int J Antimicrob Agents* 2016;47:210–6.