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Original Article

Treatment of Uncomplicated Recurrent Urinary Tract Infection with Chinese Medicine Formula: A Randomized Controlled Trial*

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ABSTRACT **Objective:** To evaluate Chinese medicine (CM) formula Bazheng Powder (八正散) as an alternative therapeutic option for female patients with recurrent urinary tract infection (RUTI). **Methods:** A randomized double-blinded trial was performed. Eligible female patients with RUTI were recruited from one hospital and two community health centers. By using a blocked randomization scheme, participants were randomized to receive a CM formula (10 herbs) and antibiotics placebo for 4 weeks, or antibiotics for 1 week followed by 3 weeks of placebo and CM formula placebo. Clinical cure rate and microbiological cure and recurrence after treatment were evaluated. **Results:** A total 122 eligible patients were enrolled, with 61 cases in each group. The clinical cure rate by the intent-to-treatment approach was 90.2% for the CM group and 82.0% for the antibiotics group ($P>0.05$). Bacteria were cleared from 88.5% (54/61) of patients in the CM group and 82.0% (50/61) in the antibiotics group. The recurrence rate in recovered patients at the 6-month follow-up was 9.1% (5/61) and 14.0 (7/61) in the CM and antibiotics groups, respectively ($P>0.05$). **Conclusion:** CM formula Bazheng Powder is a good alternative option for RUTI treatment. (Registration No. NCT01745328)

KEYWORDS Chinese medicine, recurrent urinary tract infection, randomized control trial

Urinary tract infection (UTI) is one of the most commonly encountered bacterial infections; approximately 40% of women and 12% of men experience at least one symptomatic episode of UTI during their lifetime, and approximately 25% of affected women suffer from recurrent UTI (RUTI).[1] RUTI usually requires the repeated use of antibiotics, promoting antibiotic resistance in the involved pathogens and rendering treatment a great challenge.[2] Management of these infections has become more complicated with the increase in antimicrobial resistance in recent years. New antimicrobial drugs are in development, but they still must face the emerging resistance. Both non-antibiotic and antibiotcis prophylaxis for recurrent tract infections have been investigated with randomized controlled trials, and acceptable efficacies obtained.[3,4] However, it is difficult for these strategies to treat ongoing RUTI. Alternative treatment options utilizing different mechanisms could alleviate or overcome these challenges.

CM has been used to treat numerous conditions including infectious disease[5,6] and was employed during the recent emergence of H1N1 avian influenza.[7] CM is also used to treat uncomplicated UTI in China.[8] However, the efficacy of CM for RUTI treatment and its relative effectiveness compared to antibiotics were not evaluated. In the present study, a randomized controlled trial was performed to evaluate the efficacy of CM for uncomplicated RUTI in women and compare the efficacy to that of antibiotics.

METHODS

Inclusion and Exclusion Criteria

Inclusion criteria included: women aged 18 to

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75 years who had a documented history of RUTI:[9] (1) at least 3 episodes of uncomplicated infection documented by urine culture with the isolation of $>10^5$ colony-forming units (CFU)/mL of a bacterial pathogen in the previous year; and (2) with clinical symptoms of dysuria, frequent urination, and/or urgency. All subjects gave written informed consent before enrollment.

The exclusion criteria include: women (1) with urinary tract dysfunction; (2) with diseases of tuberculosis, urinary tract anatomical abnormalities, obstructive renal pelvis and ureter hydronephrosis; (3) with menstruation, pregnancy and lactation; (4) with severeious complications of blood vessels, liver and kidneys, as well as mental patients; (5) has received the relevant treatment that may affect diagnosis or determine the efficacy of persons; (6) has high fever, chills, severe bacteremia and other systemic manifestations.

Study Design

The study was conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki, and the protocols were approved by the Human Subject Review Board of Wangjing Hospital, Chinese Academy of Chinese Medicine (No. 20090012). The study was registered at clinicalTrials.gov on December 7, 2012 (Identifier NCT01745328).

Patients were recruited from one hospital (Wangjing Hospital) and two community health centers (Wangjing Community Health Service Center and Wangjing East Lake Community Health Service Center). At the initial medical visit, potential participants underwent an interview using a standardized study questionnaire and a midstream urine specimen collection to evaluate bacteriuria. Urine samples from the two communities were sent to Wangjing Hospital for bacteria culture, isolation and resistance analysis. Eligible patients were enrolled and subjected to either of the CM or antibiotics treatments. Participants were randomized to treatment assignments by the statistician using a blocked randomization scheme with varying block sizes not revealed to clinic personnel. A computer statistics package was used to randomly generate the intervention/control list. This list was accessible only to one member of the administrative staff who had no other involvement in the study and allocated treatment in a sequential fashion. Assignments were placed in sealed, sequentially numbered envelopes, which were opened at the time of enrollment. Enrolled patients were followed up for their adherence to treatment, and data were collected by the investigators who carried out the treatments.

Sample Size Estimation

A non-inferiority approach was used to evaluate the efficacy of CM. Efficacy data were based on previously reported data and our own clinical experience. Using a 10% type Ⅰ error, an 85% power, and proposing the hypothesis that CM and antibiotic treatments would be effective in at least 90% of patients, the sample size estimation indicated that 50 subjects per group were adequate to test the non-inferiority hypothesis. A 10% dropout rate was estimated; therefore, a total 60 patients were enrolled into each treatment group.

Treatment

Participants of the CM group were given granules of CM and antibiotics placebo, and the antibiotics group was given granules of antibiotics and CM placebo. Each treatment bag was labeled a sequential number and contains both CM/CM placebo granules, and antibiotics/antibiotics placebo capsules. Antibiotics or its placebo were manufactured as capsules labeled as A [levofloxacin (LVX) or placebo], B [amoxicillin/clavulanic acid (AMX) or placebo], and C (placebo) with identical appearance. Granule A was used 200 mg twice daily, and B 500 mg 3 times daily for 1 week, followed by 3 weeks of granule C. Granule A and C were used when uropathogen was sensitive LVX, otherwise B and C were used. When resistant to both antibiotics, another sensitive antibiotics and C were used. For CM treatment, patients were administered CM twice daily for 4 weeks. The CM formula was derived from an ancient remedy (Bazheng Powder, 八正散) officially recorded in Song Dynasty and comprised 10 herbs (116 g): *Anemarrhena asphodeloides* Bunge (15 g), *Platycladus orientalis* (L.) Franco (10 g), *Angelica sinensis* (Oliv.) Diels (10 g), *Rehmannia glutinosa* (Gaertn.) DC. (15 g), *Poria cocos* (Schw.) Wolf (15 g), *Salvia miltiorrhiza* Bunge (10 g), *Rheum palmatum* L. (6 g), *Polygonum aviculare* L. (10 g), *Dianthus superbus* L. (10 g), and *Talcum* (15 g). This formula has been proven to be effective by both clinical practice and experimental studies.[8,10] The formula particles (lot No. 20100219) were produced by Jiangying Tianjiang Pharmaceutical

Chin J Integr Med 2019 Jan;25(1):16-22

Co., Ltd. (China). The placebo was also produced as particle with identical shape and taste to make sure participates could not differentiate the two particles. To make sure that the patients have taken their treatments, they were required to return the drug bags.

Outcome Measures

The primary outcome was clinical recovery. The secondary outcomes were the uropathogen clearance and the incidence of UTI recurrence. After 4 weeks of treatment, the symptoms, presence of uropathogens, and hepatorenal function were examined and recorded. Patients were followed up for 6 months after the last treatment to detect disease recurrence. Recurrence of symptoms was recorded for the clinical cured patients. Treatment responses were defined as the disappearance or improvement of clinical symptoms, and uropathogen clearance. Since RUTI is difficult to completely cure, clinical treatment outcomes were categorized into 4 outcomes: complete cure (symptoms completely cured), significant recovery (over 70% of the symptoms cured), symptomatic improvement (over 30% of the symptoms cured), and treatment failure (less than 30% symptom cure or no response).[11] Each symptom are quantified by a 5-point scale, where 0, 2, 4, 6 and 8 represent no, seldom, occasional, half time and always frequency. Symptom treatment efficiency was divided into complete recovery (⩾95%), significant recovery (70%–94%), improvement (30%–69%) and invalid (<30%). The clinical cure was defined as over 70% symptom score reduction or uropathogen clearance. Safety and side effects were monitored by detection of alanine aminotransferase, aspartate aminotransferase and creatinine both before and after the treatment.

Statistical Analysis

The statistical analysis included all randomized subjects who completed the scheduled visits (intention to treat). The Student *t*-test was used to analyze continuous variables. Categorical variables were analyzed with the chi-square test or Fisher exact test, as appropriate. Primary quantitative outcome variables were compared by the Student *t*-test or the Mann-Whitney U test, as appropriate. Treatment efficiency was calculated as the clinical cure rate of recovered patients who showed bacterial clearance or over 70% symptom reduction. Three analytical approaches, including intend-to-treatment (ITT), per-protocol (PP), and non-response-to-treatment (NRT), were used to analyze the treatment efficacies. Two-sided *P* values were calculated. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Study Population

The patient enrollment and follow-up periods occurred between 2010 and 2013. A total 186 women were assessed for eligibility according to the inclusion and exclusion criteria. Fifty-two women were ineligible, and 12 otherwise eligible individuals refused to participate in the study. In total, 122 eligible women were enrolled and randomized to receive treatment (Figure 1). One woman in the antibiotics group and 2 in the CM group were lost to follow-up 4 weeks after completing treatment. Eleven women in the CM group and 13 women in the antibiotics groups were lost to follow-up at the recheck examination performed 6 months post-treatment.

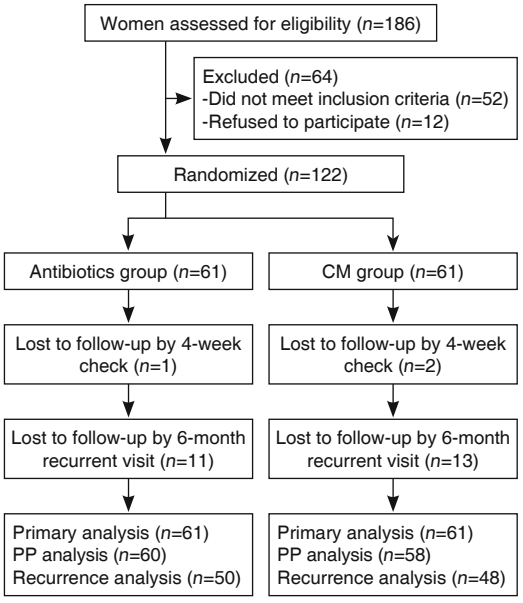

Figure 1. RUTI Patient Enrollment and Outcome

The baseline demographic and disease characteristics were similar between the two groups (*P*>0.05, Table 1). Over 80% of the patients experienced frequent or urgent urination, or both symptoms. Leukocytes and urine protein were detected on urinalysis in 50 patients. Uropathogens were isolated in over 93.4% of patients at the first urine culture.

Bacterial uropathogens were isolated from over 93.4% of the enrolled patients. In the majority of cases, *E. coli* alone was isolated; *E. coli* was isolated in combination with another uropathogen in a minority

Table 1. Demographic and Clinical Characteristics of RUTI Participants at Enrollment

Item	CM (61 cases)	Antibiotics (61 cases)
Demographic characteristics ($\bar{x} \pm s$)		
Age (Year)	53.93 ± 17.00	55.59 ± 16.89
Duration (Day)	7.42 ± 6.77	7.08 ± 8.66
Disease history (Month)	4.73 ± 6.12	5.08 ± 6.68
Recurrence time	4.17 ± 2.94	4.07 ± 2.37
Disease characteristics [Case (%)]		
White blood cells	56 (91.8)	51 (83.6)
Urine protein	54 (88.5)	50 (82.0)
Uropathogen culture	57 (93.4)	59 (96.7)
Urine frequency	56 (91.8)	58 (95.1)
Urinary urgency	54 (88.5)	50 (82.0)
Urinary pain	46 (75.4)	50 (82.0)

Table 2. Uropathogen Identity and Sensitivity to Antibiotics [Case (%)]

Uropathogen identity and sensitivity	CM (61 cases)	Antibiotics (61 cases)
Uropathogen species		
E. coli	38 (62.3)	38 (62.3)
Staphylococcus	6 (9.8)	6 (9.8)
Enterococcus	5 (8.2)	4 (6.6)
Klebsiella pneumonia	4 (6.6)	3 (4.9)
Proteus mirabilis	1 (1.6)	3 (4.9)
Streptococcus	0	3 (4.9)
Others	7 (11.5)	4 (6.6)
Uropathogen concentration		
No growth	4 (6.6)	2 (3.3)
10^2 to $<10^5$	4 (6.6)	5 (8.2)
$\geqslant 10^5$	53 (86.9)	54 (88.5)
Sensitivity to treatment antibiotics		
Amoxicillin/clavulanic acid	44 (86.3)	48 (90.6)
Levofloxacin	26 (42.0)	33 (58.0)

of cases. The remaining RUTIs were caused by *Staphylococcus*, *Klebsiella pneumonia*, *Enterococcus*, *Proteus mirabilis*, and *Streptococcus*. *E. coli* were isolated from 62.3% of patients in both groups. Over 86% of patients showed $\geqslant 10^5$ CFU/mL urine at enrollment. The isolated uropathogens were highly sensitive to AMX, with 86.3% of the CM group and 90.6% of the antibiotics group isolates sensitive to AMX. The isolates were less sensitive to LVX, with 42.0% and 58.0% of isolates sensitive in the CM and antibiotics groups, respectively (Table 2). Therefore, in most cases, the two antibiotics were applicable for treatment.

The resistance profiles of the uropathogens to 18 common antibiotics were analyzed (Table 3). The isolates showed multiple drug resistance. All 9 enterococcus strains were resistant to 2 antibiotics, and 44.4% were resistant to at least 5 antibiotics. Comparison of the isolates between the two treatment groups showed different multiple antibiotic resistance profiles without any significant differences. Extended-spectrum β-lactamases (ESBLs) were detected in 12 of the isolates, 5 in the antibiotics group and 7 in the CM group.

Primary Outcome

The effective treatment rate with an ITT approach

Table 3. Antibiotic Resistance Profiles of Isolated Uropathogens [Case (%)]

Uropathogen species/group comparison	Drug resistance number			
	1	2	3	5
Uropathogen species				
E. coli	58 (76.3)	58 (76.3)	36 (47.4)	31 (40.8)
Klebsiella pneumoniae	2 (28.6)	2 (28.6)	2 (28.6)	2 (28.6)
Enterococcus	9 (100.0)	9 (100.0)	4 (44.4)	4 (44.4)
Staphylococcus	8 (66.7)	8 (66.7)	7 (58.3)	5 (41.7)
Streptococcus	2 (66.7)	2 (66.7)	2 (66.7)	1 (33.3)
Proteus mirabilis	1 (25.0)	1 (25.0)	0	0
Other	6 (54.5)	6 (54.5)	6 (54.5)	5 (45.5)
Total	86 (70.5)	86 (70.5)	57 (48.3)	48 (40.7)
Antibiotics group *vs*. CM group				
Antibiotics	40 (65.6)	40 (65.6)	30 (49.2)	26 (42.6)
CM	46 (75.4)	46 (75.4)	27 (44.3)	22 (36.1)
χ^2 (*P*)	1.419 (0.236)	1.419 (0.236)	0.296 (0.586)	0.550 (0.458)

Chin J Integr Med 2019 Jan;25(1):16-22

in which patients lost to follow-up were considered to have achieved a clinical cure was 95.1% in the antibiotics group compared to 96.7% in the CM group. The two groups showed similar primary outcomes. However, the therapeutic efficacy differed between the two groups. Approximately 30% of patients were completely clinically cured in both groups; however, the CM group showed a significantly higher rate of significant cure than the antibiotics group (47.5% *vs*. 26.2%, $P<0.05$), and the antibiotics group showed a higher rate of symptomatic improvement than the CM group (39.3% *vs*. 18.0%, $P<0.05$, Table 4).

Table 4. Primary Treatment Outcomes of RUTI Patients [Case (%)]

Item	CM (61 cases)	Antibiotics (61 cases)
Primary clinical outcomes*		
Complete cure	19 (31.1)	18 (29.5)
Significant cure	29 (47.5)	16 (26.2)*
Symptomatic improvement	11 (18.0)	24 (39.3)*
Treatment failure	2 (3.3)	3 (4.9)
Clinical cure		
ITT	55 (90.2)	50 (82.0)
PP	53 (89.8)	50 (81.7)
NRT	53 (86.9)	49 (80.3)

Note: *$P<0.05$ *vs*. CM group

In the ITT method, patients lost to follow-up were considered clinically cured, and the resulting treatment efficacy was 90.2% and 82.0% for the CM and antibiotics groups, respectively ($P>0.05$). Using the NRT method, patients lost to follow-up were considered to have no response to treatment, and the treatment efficacy was 86.9% for the CM group and 80.3% for the antibiotics group. In general, the treatment efficacy did not differ significantly between the two groups according to the analytical method, although the CM group showed a slightly higher efficacy than the antibiotics group.

Secondary Outcome

At the end of the treatment, the uropathogen was cleared in 53 (88.3%) of the CM patients, which was higher than observed in the antibiotics group at 47 (77.0%) patients. Only 2 patients in the CM group and 8 patients in the antibiotics group showed a decreased concentration (10^2 to $<10^5$ CFU/mL) of uropathogens in the urine (Table 5). Therefore, in most cases, the bacteria were cleared from the patients. The CM group showed greater bacterial clearance than the antibiotics group, although this difference was not significant. In all three methods of ITT, PP, and NRT, the clearance rates were greater than 80%, and it was slightly higher in the CM group than that in the antibiotics group; however, no significant difference was observed between the two groups in any of the three analytical methods ($P>0.05$).

Table 5. Secondary Treatment Outcomes of RUTI Patients [Case (%)]

Item	CM	Antibiotics
Uropathogen isolation at the end of treatment		
No growth	53 (88.3)	47 (77.0)
10^2 to $<10^5$	2 (3.3)	8 (13.1)
$\geqslant 10^5$	5 (8.3)	6 (9.8)
Bacterial clearance		
ITT	54 (88.5)	50 (82.0)
PP	52 (88.1)	49 (81.7)
NRT	52 (88.1)	49 (80.3)
Patients of follow-up		
ITT	8 (13.1)	12 (19.7)
PP	8 (16.0)	12 (25.0)
NRT	19 (31.1)	25 (41.0)
Recurrence in recovered patients		
ITT	5 (9.1)	7 (14.0)
PP	4 (9.1)	7 (18.4)
NRT	16 (30.8)	23 (46.9)

During the 6-month follow-up, 11 patients were lost to follow-up in the CM group and 13 in the antibiotics group. According to the ITT method, the recurrence rate was 13.1% in the CM group, compared to 19.7% in the antibiotics group. In all three methods, the recurrence rate was lower in the CM group than in the antibiotics group. The recurrence rate (ITT) in the recovered patients was 9.1% in the CM group and 14.0% in the antibiotics group. No significant differences were observed between the two groups in the recurrence rates for the clinically cured patients.

Safety

No significant side effects were observed in both groups (data not shown).

DISCUSSION

Uncomplicated RUTI represents a great challenge for treatment using antibiotics due to the need for repeated antibiotic use and the emergence of multi-drug or pan-drug resistant uropathogens.[12] CM is an ancient treatment strategy employing a mechanism different

from that of antibiotics and has been proven effective in treating infectious disease.[13] CM is also an option for the treatment of uncomplicated RUTI.[8] However, until now, the therapeutic efficacy of CM, particularly compared to antibiotics in a controlled trial, has not been evaluated. In this randomized antibiotic-controlled trial, we have demonstrated that uncomplicated RUTI could be effectively treated with CM.

The present study aimed to determine whether CM is comparable or non-inferior to antibiotics in the treatment of RUTI. Using this statistical approach, along with clinical experience, 90% of the patients were expected to respond to treatment. Therefore, a sample size of 50 patients per group was sufficient for the study. A total of 61 patients were enrolled in each group, and at the end of follow-up, 50 patients were analyzed. The demographics and disease characteristics of the patients were comparable between the CM and antibiotics groups upon enrollment. Uropathogens were isolated from over 93% of patients, and *E. coli* was the most represented uropathogen (62.3%). Resistance analysis showed that 70.5% of the isolates were resistant to at least one antibiotic, and 48.3% were multi-drug resistant. This finding is consistent with previous reports of resistance prevalence.[12] Based on our clinical experience, two antibiotics were selected, AMX and LVX. Fortunately, the two antibiotics chosen for the study showed relatively high sensitivity. Over 80% of the isolates were sensitive to AMX; therefore, most of the enrolled patients were treated with AMX.

During the RUTI treatment, the clinical cure rate did not reach 100%.[14] Thus, to better compare the two treatment strategies, in addition to calculating the overall efficacy, we further divided the main outcomes into 4 categories. Although the clinical cure rate of the CM and antibiotics groups did not differ significantly, the CM group showed greater significant cure than the antibiotics group. In CM, RUTI is placed in the stranguria category;[15] the basic pathogenesis of this category is a yin deficiency of Gan (Liver) and Shen (Kidney), or a yang deficiency of Shen and Pi (Spleen), manifested by dysfunction of bladder and kidney. To treat RUTI, the CM formula does not directly target the uropathogen; it is designed to reverse the dysfunction to a healthy status. CM treatment not only reverses the patient from a diseased state to a healthy state, but also improves immune function.[16] Several studies have shown that CM treatment modulates the ability of the patient to resist hostile environments.[17] Although carried out in mice, these studies provide some evidence for the possible mechanism of CM treatment. Therefore, it is possible that CM treatment can not only clear the bacteria, but also improve the symptoms. In the CM group, 88.3% of patients did not show any bacteria in the urine, which was slightly higher than the 77.0% observed in the antibiotics group. In the antibiotics group, a significantly high percentage of patients showed a persistently low concentration of bacteria in the urine. Although there was no significant difference observed in the bacterial isolation frequency, CM showed good efficacy at bacterial clearance. This result was interesting because CM does not target the uropathogen, but instead targets the host immune status.[8] Potentially, this may be because CM enhances the health condition of the patient, which improves the capability to clear invading uropathogens.

Recurrence is an important parameters for evaluation of RUTI treatment efficacy.[18] Recurrence at 6 months post-treatment was assessed at a follow-up examination. In total, 13 and 11 patients were lost to follow-up in the CM and antibiotics groups, respectively; these patients were excluded from the recurrence rate analysis. Four patients in the CM group and 7 in the antibiotics group initially significant recovery but later showed relapse. When all the patients in the follow-up survey were designated as the denominator, the recurrence rate in the CM group was significantly lower than that in the antibiotics group (13.1% *vs*. 19.7%). This difference was more significant when the recurrence rate was calculated in patients with significant recovery (9.1% *vs*. 14.0%). Due to the limitation of small sample size, the prevention of recurrence by CM could not be evaluated statistically. The recurrence rate of CM is lower than that of antibiotics, although not statistically significant. Large sample of clinical trials might prove this. Another limitation of the present study is that only women patients were enrolled, for over 80% of RUTI patients were female. Therefore, whether the CM formula Bazheng Powder could be applied to male patients needs to be further confirmed.

Compared with antibiotics, CM treatment needs a longer duration to cure the infection. Because treatment with antibiotics could not efficiently prevent recurrence, and usually result in resistance, CM could complement the antibiotics. Therefore, most of the enrolled patients are willing to accept CM treatment. Another reason

came from the fact that in China, CM is a common treatment option with acceptable efficacy.

Taken together, the present randomized antibiotics-controlled trial shows that CM can treat uncomplicated RUTI. Compared to antibiotics CM treatment showed a higher rate of complete cure and significant recovery at the end of treatment. CM treatment had a lower rate of recurrence in the patients showing recovery. CM not only effectively treated uncomplicated RUTI, but also prevented recurrence. In clinical practice, many patients have allergies or intolerance to penicillin and other antibiotics, and therefore the CM approach may be helpful for this subpopulation. Therefore, CM is a good alternative option for treatment of uncomplicated RUTI.

Conflict of Interests

The authors have no financial associations or any other conflicts of interests to declare.

Author Contributions

CZL, ZN, and LSW conceptualized and designed the study. LSW and GJ contributed to data collection or interpretation. WW contributed to data interpretation and manuscript preparation. CZL and LSW drafted the paper. CZL and ZN had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final version of the paper.

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REFERENCES

1. Foxman B. The epidemiology of urinary tract infection. Nature Rev Urol 2010;7:653-660.
2. Hooton TM. Uncomplicated urinary tract infection. N Engl J Med 2012;366:1028-1037.
3. Beerepoot MA, Geerlings SE, van Haarst EP, van Charante NM, ter Riet G. Nonantibiotic prophylaxis for recurrent urinary tract infections: a systematic review and meta-analysis of randomized controlled trials. J Uroly 2013;190:1981-1989.
4. Stapleton AE, Au-Yeung M, Hooton TM, Fredricks DN, Roberts PL, Czaja CA, et al. Randomized, placebo-controlled phase 2 trial of a Lactobacillus crispatus probiotic given intravaginally for prevention of recurrent urinary tract infection. Clin Infect Dis 2011;52:1212-1217.
5. Jiang WY. Therapeutic wisdom in traditional Chinese medicine: a perspective from modern science. Discov Med 2009;5:455-461.
6. Han JN. Treatment of influenza: Chinese medicine *vs*. Western medicine. J Thoracic Dis 2012;4:10-11.
7. Wang C, Cao B, Liu QQ, Zou ZQ, Liang ZA, Gu L, et al. Oseltamivir compared with the Chinese traditional therapy Maxingshigan-Yinqiaosan in the treatment of H1N1 influenza: a randomized trial. Annal Intern Med 2011;155:217-225.
8. Zhang N, Huang L, Liu S, Wang Y, Luo Y, Jin X, et al. Traditional Chinese medicine: an alternative treatment option for refractory recurrent urinary tract infections. Clin Infect Dis 2013;56:1355.
9. Gupta K, Hooton TM, Roberts PL, Stamm WE. Patient-initiated treatment of uncomplicated recurrent urinary tract infections in young women. Annal Intern Med 2001;135:9-16.
10. Liu SW, Xu XY, Xu J, Yuan JY, Wu WK, Zhang N, et al. Multi-drug resistant uropathogenic *Escherichia coli* and its treatment by Chinese medicine. Chin J Integr Med 2016.
11. Zheng XY, ed. Guiding principles of clinical research on traditional Chinese drugs. Beijing: China Medic-Pharmaceutical Sciences and Technology Publishing House; 2002.
12. Liu S, Zhang N, Chen Z. Recurrent urinary tract infections caused by multidrug-resistant uropathogenic *Escherichia coli*: implications for diagnosis and treatment. Eur Urol 2013;63:410-411.
13. Leung WK, Wu JC, Liang SM, Chan LS, Chan FK, Xie H, et al. Treatment of diarrhea-predominant irritable bowel syndrome with traditional Chinese herbal medicine: a randomized placebo-controlled trial. Am J Gastroenterol 2006;101:1574-1580.
14. Hooton TM, Roberts PL, Stapleton AE. Cefpodoxime *vs* ciprofloxacin for short-course treatment of acute uncomplicated cystitis: a randomized trial. JAMA 2012;307:583-589.
15. Jiang M, Zhang C, Zheng G, Guo H, Li L, Yang J, et al. Traditional Chinese medicine Zheng in the era of evidence-based medicine: a literature analysis. Evid Based Complement Alternat Med 2012;2012:409568.
16. Lu NN, Liu Q, Gu LG, Ge SJ, Wu J, Ze-Ji Q, et al. Gene Expression profiles underlying selective T-cell-mediated immunity activity of a Chinese medicine granule on mice infected with influenza virus H1N1. Evid Based Complement Alternat Med 2014;2014:976364.
17. Chen L, Fan J, Li Y, Shi X, Ju D, Yan Q, et al. Modified Jiu Wei Qiang Huo decoction improves dysfunctional metabolomics in influenza A pneumonia-infected mice. Biomed Chromatogr 2014;28:468-474.
18. Mori R, Lakhanpaul M, Verrier-Jones K. Diagnosis and management of urinary tract infection in children: summary of NICE guidance. BMJ 2007;335:395-397.

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