

Effects of Gegen Qinlian Decoction combined with Chinese herbal hot package on the expression of PCT, CRP and IL-6 in patients with acute gastroenteritis

Weiwei Zhang¹, Mei Yang¹, Stephan Rietz², Pei Li^{3*}

¹Department of Preventive Treatment of Disease, Hospital of Chengdu University of TCM, Chengdu 610072, Sichuan Province, China

²Department of Dermatology, University Medical Center Mainz, Langenbeckstrasse 1, D-55131 Mainz, Germany

³Department of Gastrology, Mianyang Hospital of TCM, Mianyang 621053, Sichuan Province, China

ARTICLE INFO

Original paper

Article history:

Received: August 05, 2021

Accepted: December 23, 2021

Published: February 28, 2022

Keywords:

AGE, Gegen Qinlian Decoction, Chinese herbal hot package, Clinical efficacy, Inflammatory factors

ABSTRACT

This study was carried out to investigate the clinical efficacy of Gegen Qinlian Decoction combined with a Chinese herbal hot package in the treatment of acute gastroenteritis (AGE), and to analyze the effects on serum PCT, CRP and IL-6 levels. For this purpose, 100 patients with AGE admitted to the hospital from January 2019 to January 2022 were selected for the study and randomly divided into observation and control groups, with 50 cases in each group. Patients in the control group were given conventional Western medical treatment, while patients in the observation group were treated with Gegen Qinlian Decoction combined with a Chinese herbal hot package on this basis. The clinical efficacy, symptom relief time, main symptom scores and serum PCT, CRP and IL-6 levels before and after treatment were compared between the two groups. Results showed that the total effective rate of patients in the observation group was significantly higher than that in the control group ($P < 0.05$). After treatment, the disappearance time of diarrhea, abdominal pain, fever and vomiting was significantly shorter in the observation group than in the control group ($P < 0.05$). After treatment, the stool properties, number of stools and abdominal pain symptom scores of patients in both groups were lower than those before treatment, and the symptom scores of patients in the observation group were lower than those in the control group ($P < 0.05$). The PCT, CRP and IL-6 levels of patients in both groups were significantly lower after treatment than before treatment, and the PCT, CRP and IL-6 levels of patients in the observation group were significantly lower than those in the control group ($P < 0.05$). It was concluded that the clinical efficacy of Gegen Qinlian Decoction combined with Chinese herbal hot package in the treatment of AGE is remarkable, which can effectively improve the clinical symptoms and reduce the inflammatory reaction of patients and is worthy of clinical promotion.

DOI: <http://dx.doi.org/10.14715/cmb/2022.68.2.27>

Copyright: © 2022 by the C.M.B. Association. All rights reserved



Introduction

AGE is an acute inflammatory disease caused by a bacterial or viral infection of the gastrointestinal mucosa, usually accompanied by acute diarrhea, abdominal pain, nausea, vomiting and fever (1-3). AGE is the highest cause of under-five mortality worldwide, especially in low- and middle-income countries (4). At present, the clinical treatment of AGE is the main symptomatic treatment of antibacterial and anti-inflammatory, which can improve the clinical symptoms of patients to a certain extent, but the efficacy of long-term use is poor, and it is easy to bring more adverse reactions. AGE belongs to the category of "vomiting" and "abdominal pain" in Chinese medicine. The pathogenesis of this disease is related to the patient's internal injury, poor diet or external invasion (5). Gegen Qinlian Decoction is one

of the classic ancient formulas, which comes from the "Treatise on Febrile Diseases" written by Zhang Zhongjing in the late Eastern Han Dynasty. This formula is mainly used for clearing heat and stopping diuresis, with the function of relieving the surface and clearing the interior. It is used for the treatment of heat and diuresis caused by internal trapping of solar surface evil (6). Chinese medicine ironing treatment is one of the external treatment methods of Chinese medicine, which refers to the treatment method of putting Chinese medicine into a container, heating it and then using the heated container to iron, roll or rub on certain parts of the body to achieve the effect of disease prevention and treatment. About ironing, the earliest recorded in *Asking Roots*• Lord Yellow's *Insides*: "disease in the bone, quenching medicine iron." and "The disease is born in the tendons, the

*Corresponding author. E-mail: 352433200@qq.com
Cellular and Molecular Biology, 2022, 68(2): 189-196

treatment is led by ironing". Chinese herbal hot package is a form of application of ironing therapy, which is mostly used clinically in the treatment of various gastrointestinal disorders in digestive system diseases (7).

At present, there are few studies on the application of Gegen Qinlian Decoction combined with Chinese herbal hot package treatment in patients with AGE, so this study aimed to explore the clinical efficacy of Gegen Qinlian Decoction combined with Chinese herbal hot package treatment for AGE and analyze the effects on serum PCT, CRP and IL-6 levels.

Materials and Methods

General information

100 patients with AGE admitted to our hospital from January 2019 to January 2022 were selected for the study. They were randomly divided into observation and control groups according to the random number table method, with 50 cases in each group. Inclusion criteria: (i) meeting the diagnostic criteria of AGE; (ii) having different degrees of fever, vomiting, abdominal pain and dehydration; (iii) patients voluntarily participated in this study and signed the informed consent form. Exclusion criteria: (i) patients with other infectious diseases; (ii) patients with allergy to the study drugs; (iii) patients with poor compliance with treatment; (iv) patients with abnormal liver and kidney function. In the treatment group, there were 32 males and 18 females, aged 25 to 65 years, with a mean of (43.54 ± 2.18) years, and the duration of disease was 1 to 4 d, with a mean of (2.42 ± 0.35) d. In the control group, there were 28 male and 22 female patients, aged 24-68 years, with a mean of (45.32 ± 3.64) years, and the duration of disease was 1-5 d, with a mean of (2.85 ± 0.42) d. There was no significant difference between the general data of the two groups ($P > 0.05$), and the study was approved by the hospital ethics committee.

Methods

Drug treatment in two groups of patients

Patients in the control group were treated with conventional Western medicine: Amoxicillin 1g/time, 2 times/d (Sichuan Aid Jian Pharmaceutical Co., Ltd., State Drug Authentication H21023908); Omeprazole 20mg /time, 2 times/d (Hainan Haili Pharmaceutical Co., Ltd., State Drug Authentication H20033510);

Clarithromycin 20mg/time, 2 times/d (Jiangxi Huiren Pharmaceutical Co., Ltd., State Drug Authentication H20033513). The treatment was continuous for 7d.

Patients in the observation group were treated with Gegen Qinlian Decoction combined with a Chinese herbal hot package based on the control group. The formula of Gegen Qinlian Decoction included 15g each of Pueraria Lobata, Honeysuckle and Poria, 10g each of Scutellaria Baicalensis and Psyllium, 6g each of Coptidis Rhizoma, Tetrapanax Papyriferus and Licorice. For those with food retention, 20g each of Divine Comedy, Malt and Hawthorn were added. For abdominal distension, 10g of rhubarb, 15g of Magnolia, 10g of Aucklandiae Radix were added. For abdominal pain, 30g of Radix Paeoniae Alba was added. In case of vomiting, 15g of Rhizoma Anemarrhenae, 20g of Bamboo Shavings were added. In case of significant fever, 10g of rhubarb was added. The dose of Chinese medicine was appropriately increased or decreased according to the patient's age and degree of illness (8). The above herbs were decocted with water and taken as one dose daily. 200ml of the soup was taken in the morning and evening for 7d. The formula of the Chinese herbal hot package included 50mg each of Semen Sinapis, Perilla Fructus, Evodia Rutaecarpa and Radish Seed. The treatment was performed by placing the 2-min heated herbal medicine in a cloth bag and then placing them on the acupuncture points of Shen Que, Tian Shu and Zhong Wan in the abdomen of the patient when the temperature was suitable. The treatment was carried out for 30 min each time, and then reheated and repeatedly applied at least 4 times for a total of 4 h.

CRP assay

CRP was detected by immunoscattering turbidimeter (Nanjing Norman Biotechnology Co., Ltd.) and CRP assay kit. All tests were performed as reagent blanks and quality control tests. Specimens can be tested only after all of them were passed. The assay was performed as follows: 250 μ L of the assay reagent polyethylene glycol was added to the EP tube, then distilled water (2 μ L) was added dropwise, and 100%, 50%, 25%, 12.5% and 6.25% of the calibration stock solution were added dropwise to the tube, all at 2 μ L. The liquid in the tube was mixed completely and treated in a water bath at 37°C. 85 μ L of the CRP

assay reagent was added dropwise to the tube. The liquid in the tubes was mixed completely and treated in a water bath at 37°C. The CRP level was measured by immunoscattering turbidimetry. CRP normal reference value ranged $\leq 10\text{mg/L}$, above this range was considered positive.

PCT and IL-6 assay

PCT was detected by Beckman AU5421 fully automated biochemistry analyzer (Beckman, USA) and PCT enzyme-linked immunofluorescence assay kit. The assay was performed as follows: The experimental reagents were equipped according to the operating instructions. The standards were diluted in 5 gradients. $10\mu\text{L}$ of standard and $40\mu\text{L}$ of the diluted sample were added to the microtiter wells and shaken at 500rp/min for 2 h. $200\mu\text{L}$ of substrate solution was added dropwise to each well and incubated for 30 min at room temperature. The plate was washed with buffer and shaken dry. After $50\mu\text{L}$ of enzyme reagent was added, the plate was sealed and incubated at room temperature (30 min). The plate was washed again and shaken dry. The color developer was added dropwise to the wells, left for 30 s, shaken well and incubated for 15 min under shade. $50\mu\text{L}$ of termination solution was added to terminate the staining. The PCT concentration in the sample was measured. The normal reference range of PCT was $<0.05\text{ng/mL}$, above this range was considered positive.

IL-6 was detected using Beckman AU5421 fully automated biochemical analyzer and IL-6 enzyme-linked immunofluorescence assay kit as above. The normal reference range of IL-6 was $<7\text{pg/mL}$, above this range was considered positive.

Observation indicators

(i) To evaluate the clinical efficacy of the two groups after treatment; (ii) To compare the disappearance time of diarrhea, abdominal pain, fever and vomiting between the two groups; (iii) To evaluate the stool properties, the number of stools and abdominal pain symptom scores before and after treatment with reference to the "Guidelines for Clinical Research on New Chinese Medicines (Trial)"; (iv) To observe the levels of CRP, PCT and IL-6. (v) Analyze the value of serum CRP and PCT levels as an aid to diagnose AGE by ROC curve.

Statistical analysis

SPSS 19.0 statistical software was used to process the data. The measurement data were expressed as ($x \pm s$) and analyzed by t-test. The statistical data were expressed as rates and analyzed by the χ^2 test. The difference was considered statistically significant at $P < 0.05$.

Results and discussion

Comparison of clinical efficacy between two groups of patients

In the observation group, 19 cases were cured, 12 cases showed an apparent effect, 15 cases were effective, and 4 cases were ineffective, with a total effective rate of 92.0%. In the control group, 8 cases were cured, 14 cases showed an apparent effect, 20 cases were effective, and 8 cases were ineffective, with an overall effective rate of 84.0%. The overall effective rate of the patients in the observation group was significantly higher than that of the control group ($P < 0.05$), as shown in Table 1 and Figure 1.

Table 1. Comparison of clinical efficacy between two groups of patients

Group	Number of cases	Cured	Apparent effect	Effective	Ineffective	Total effective rate
Observation	50	19 (38%)	12 (24%)	15 (30%)	4 (8%)	46 (92.0%)
Control	50	8 (16%)	14 (28%)	20 (40%)	8 (16%)	42 (84.0%)
χ^2						12.946
P						<0.05

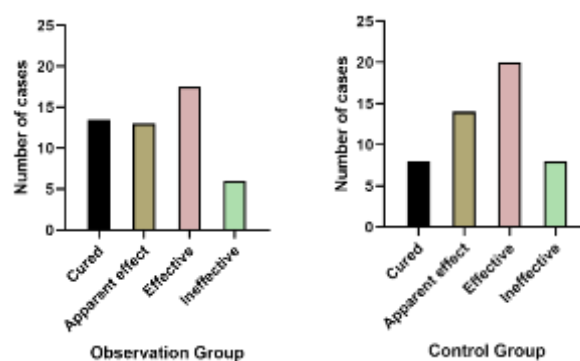


Figure 1. Comparison of clinical efficacy between two groups of patients

Comparison of the time of symptom relief between the two groups

The time of disappearance of diarrhea, abdominal pain, fever and vomiting in the observation group was significantly shorter than that in the control group ($P < 0.05$), see Table 2 and Figure 2.

Table 2. Comparison of time to symptom relief between two groups of patients

Group	Number of cases	Abdominal pain	Diarrhea	Fever	Vomiting
Observation	50	16.82±2.35	20.63±4.54	10.34±2.08	8.37 ± 1.66
Control	50	23.26±4.58	28.38±6.25	16.24±3.89	14.26 ± 2.94
t		5.397	8.428	6.183	8.316
P		<0.05	<0.05	<0.05	<0.05

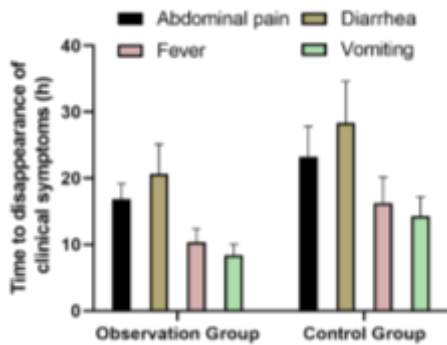


Figure 2. Comparison of symptom relief time between the two groups of patients

Comparison of symptom scores between the two groups

The symptom scores of stool properties, stool frequency and abdominal pain in both groups were lower after treatment than before treatment, and the symptom scores of patients in the observation group were lower than those in the control group (P<0.05), see Table 3.

Table 3. Comparison of symptom scores between the two groups

Group	Number of cases	Stool properties		Stool frequency		Abdominal pain	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Observation	50	4.15 ± 0.62	0.81 ± 0.16*#	3.85 ± 0.58	0.86 ± 0.12*#	3.86 ± 0.87	0.85 ± 0.16*#
Control	50	4.13 ± 0.64	1.46 ± 0.23*	3.78 ± 0.52	1.63 ± 0.32*	3.78 ± 0.82	1.58 ± 0.37*

Note: Compared with pre-treatment, * P < 0. 05; compared with post-treatment control group, # P < 0. 05

Table 4. Changes in serum PCT concentrations on days 1, 3, 5, and 7 of admission in the two groups (ng/ml,x±s)

Group	Number of cases	Day 1	Day 3	Day 5	Day 7
Observation	50	2.57±0.73	0.75±0.40*	0.62±0.37**	0.59±0.66***
Control	50	2.64±0.84	1.70±0.76#	1.48±0.54###	1.45±0.79###
F		7.354	65.820	38.285	46.020
P		>0.05	<0.05	<0.05	<0.05

Note: * indicates the comparison with day 1 of admission in the observation group, P<0.05; ** indicates the comparison with day 3 in the observation group, P<0.05; *** indicates the comparison with day 5 in the observation group, P>0.05. # indicates the comparison with day 1 of admission in the control group, P<0.05; ## indicates the comparison with day 3 in the control group, P<0.05; ### indicates the comparison with day 5 in the control group, P>0.05.

Changes in serum PCT concentrations on days 1, 3, 5, and 7 of admission in the two groups

At the time of admission, serum PCT levels in the two groups were not statistically significant (P<0.001). With the pro-treatment intervention, PCT levels gradually decreased on the 1st, 3rd, 5th and 7th days of admission. The differences were statistically significant (P<0.05), except for the differences between day 7 and day 5, which were not statistically significant (P>0.05). The PCT levels of patients in the observation group were significantly lower than those in the control group (P<0. 05), as shown in Table 4 and Figure 3a.

Changes in serum IL-6 concentrations on days 1, 3, 5, and 7 of admission in the two groups

At the time of admission, serum IL-6 levels in both groups were not statistically significant (P<0.001). With the pro-treatment intervention, the PCT levels gradually decreased on the 1st, 3rd, 5th and 7th days of admission, and the differences were statistically significant (P<0.05). And the PCT levels of patients in the observation group were significantly lower than those in the control group (P<0. 05), as shown in Table 5 and Figure 3b.

Table 5. Comparison of the differences in IL-6 between the two groups at different times (pg/ml, x±s)

Group	Number of cases	Day 1	Day 3	Day 5	Day 7
Observation	50	36.83±5.62	21.75±0.40*	12.62±0.37**	9.59±0.66***
Control	50	36.75±5.34	28.70±0.76#	23.48±0.54##	18.45±0.79###
F		15.354	46.536	85.939	168.314
P		>0.05	<0.05	<0.05	<0.05

Note: * indicates the comparison with day 1 of admission in the observation group, P<0.05; ** indicates the comparison with day 3 in the observation group, P<0.05; *** indicates the comparison with day 5 in the observation group, P>0.05. # indicates the comparison with day 1 of admission in the control group, P<0.05; ## indicates the comparison with day 3 in the control group, P<0.05; ### indicates the comparison with day 5 in the control group, P<0.05.

Changes in serum CRP concentrations at 1, 3, 5 and 7 days of admission in both groups

At the time of admission, there was no statistically significant difference between the serum IL-6 levels of the two groups ($P < 0.001$). With the pro-treatment intervention, the PCT levels gradually decreased on day 1, day 3, day 5 and day 7 of admission with statistically significant differences ($P < 0.05$), and the PCT levels of patients in the observation group were significantly lower than those in the control group ($P < 0.05$), as shown in Table 6 and Figure 3c.

Table 6. Changes in serum CRP concentrations at 1, 3, 5 and 7 days of admission in both groups (pg/ml, $\bar{x} \pm s$)

Group	Number of cases	Day 1	Day 3	Day 5	Day 7
Observation	50	45.63±9.43	30.75±8.32*	22.62±5.43**	15.59±7.57***
Control	50	45.57±9.36	38.70±6.97#	30.48±6.86###	26.45±8.69###
F		10.882	46.826	54.621	80.592
P		>0.05	<0.05	<0.05	<0.05

Note: * indicates the comparison with day 1 of admission in the observation group, $P < 0.05$; ** indicates the comparison with day 3 in the observation group, $P < 0.05$; *** indicates the comparison with day 5 in the observation group, $P > 0.05$. # indicates the comparison with day 1 of admission in the control group, $P < 0.05$; ## indicates the comparison with day 3 in the control group, $P < 0.05$; ### indicates the comparison with day 5 in the control group, $P < 0.05$.

Comparison of PCT, CRP and IL-6 levels between two groups of patients

The levels of PCT, CRP, and IL-6 in both groups were significantly lower after treatment than before treatment, and the levels of PCT, CRP, and IL-6 in the

observation group were significantly lower than those in the control group ($P < 0.05$), as shown in Table 7.

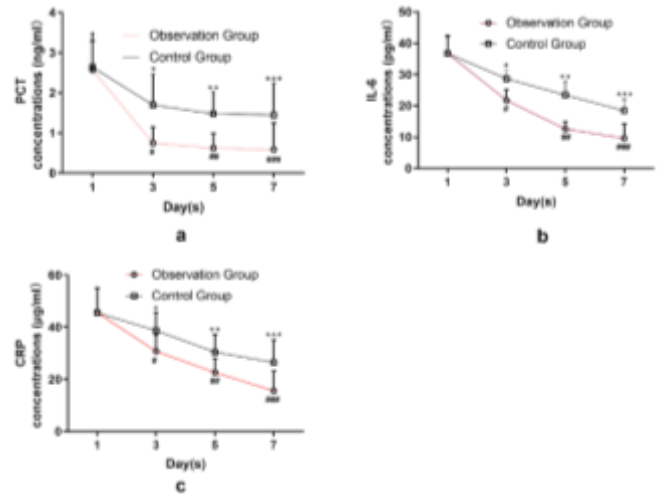


Figure 3. Changes in PCT (a), IL-6 (b), and CRP (c) serum concentrations after 1, 3, 5, and 7 days of treatment in both groups

Value of ROC curve analysis of serum CRP and PCT levels to assist in the diagnosis of AGE

In the ROC analysis, the area under the curve was 0.93 (95% confidence interval: 0.85-0.97) for PCT, 0.84 (95% confidence interval: 0.73-0.91) for CRP, and 0.64 (95% confidence interval: 0.45-0.80) for interleukin 6. Calcitonin concentration was the best way to distinguish bacterial from viral infections, above CRP or interleukin 6, as shown in Figure 4.

Table 7. Comparison of PCT, CRP and IL-6 levels between two groups of patients

Group	Number of cases	PCT (ng /ml)		CRP (µg /ml)		IL-6 (pg /ml)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Observation	50	2.57±0.73	0.53±0.12*#	45.63±9.43	14.62±6.69*#	36.83±5.62	8.14±5.67*#
Control	50	2.64±0.84	1.35±0.09*	45.57±9.36	25.21±10.43*	36.75±5.34	17.22±6.13*

Note: Compared with pre-treatment, * $P < 0.05$; compared with post-treatment control group, # $P < 0.05$.

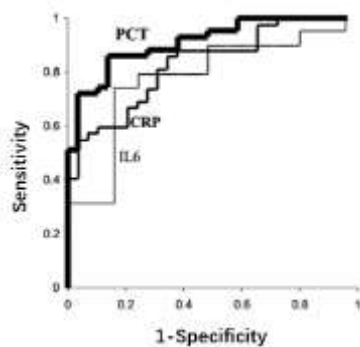


Figure 4. ROC curve analysis of serum CRP and PCT levels to assist in the diagnosis of AGE value

AGE is associated with considerable morbidity and mortality worldwide. Early identification of the cause may prevent unnecessary antibiotic use and reduce morbidity and mortality. However, it is not always possible to distinguish between viral and bacterial infections based on clinical features and laboratory tests such as fecal occult blood and white blood cells. The production of inflammatory cytokines and proteins in the acute phase usually correlates with the severity of bacterial infection (9).

The elevated IL-6 plasma concentrations are present early in the inflammatory process (10,11) and IL-6 levels correlate with the severity of sepsis and inflammation (12). IL-6 plays a major role in the induction of synthesis of acute-phase proteins such as CRP and LBP (13). Therefore, IL-6 is a potentially interesting marker for evaluation in the early stages of infection. A study by Chien-Hung Lin showed that IL-6 production was increased in intestinal mucosa and intestinal epithelium during acute phase inflammation (14). L. Joshi's study also showed that viral and bacterial infectious diseases can lead to elevated interleukin (IL)-6 and tumor necrosis factor (TNF)- α in the serum of patients (15) CRP (CRP) is the best known acute temporal protein and is usually accompanied by elevated blood levels of CRP in human inflammation and infection. CRP mediates the onset of phagocytosis by labeling damaged cells. This labeling leads to activation of the classical complement pathway and the eventual elimination of pathogens or cell death. Borgnolo, to differentiate between bacterial and viral infections, serum CRP levels were studied in three groups of children under 5 years of age with gastroenteritis. The results suggest that the determination of CRP values can be a useful tool for predicting bacterial gastroenteritis in pediatric patients (16). Nufar Marcus performed CRP testing, blood tests and stool cultures in 44 children with gastroenteritis who presented to the emergency department. The results suggest that the CRP test appears to be a useful predictor of bacterial gastroenteritis in children. Therefore, it becomes a promising tool in emergency departments to control infections and help physicians in antibiotic therapy decisions (17).

PCT, a prohormone of calcitonin, has been evaluated as a marker for the diagnosis of bacterial infections. It has higher specificity and sensitivity in distinguishing bacterial from non-infectious causes of inflammation compared to CRP and correlates with disease severity and patient prognosis (18). A study by Kelvin showed that PCT expression was significantly increased in infectious gastroenteritis and could be used as a diagnostic indicator of bacterial AGE (19). Ana Belen conducted a 7-month prospective study of children diagnosed with AGE in the emergency room and showed that PCT was elevated in bacterial gastroenteritis, as was CRP (20).

At present, the clinical treatment of AGE is the mainly symptomatic treatment of antibacterial and anti-inflammatory. Although it can improve the clinical symptoms of patients to a certain extent, the long-term use of the efficacy is poor, and it is easy to bring more adverse reactions. Antoniazzi reported a case of persistent impairment of consciousness after administration of oxamide in a patient with gastroenteritis (21). Sulkers et al. described the side effects of acute urinary retention following the use of antiemetics in patients with AGE (22).

In ancient medicine, medicines were made from plants. Medicinal plants are classified into certain groups according to their scope of action. A medicinal plant does not always have a definite effect and the range of its effects may be more or less. This means that one plant may be effective in treating several diseases; Conversely, to enhance their therapeutic effect, a mixture of several plants is often prepared to multiply their effect (23-27).

Chinese medicine is concerned with "treating both the symptoms and the root cause". Traditional Chinese medicine continues to introduce treatment options such as Chinese herbal soup or Chinese physical therapy to treat acute inflammation. The principles of TCM treatment for AGE are based on removing dampness and evil, eliminating food and harmonizing the stomach. It is well documented in the Treatise on Febrile Diseases that *Gegen Qinlian Decoction* has the effect of relieving the exterior and clearing the interior as well as harmonizing the stomach. It is mostly used to treat conditions such as lowering heat and diuresis (28). As a characteristic therapy for pain relief in Chinese medicine, the Chinese herbal hot package has the advantages of convenience, safety and effectiveness. It is widely used clinically for the treatment of various pain conditions but is less commonly used in abdominal pain caused by AGE (7). The effective rate of patients in the observation group was significantly higher than that of the control group. The disappearance time of diarrhea, abdominal pain, fever and vomiting in the observation group was significantly shorter than that in the control group. The stool properties, number of stools and abdominal pain symptom scores of patients in both groups after treatment were lower than those before treatment, and the symptom scores of patients in the observation group were lower than those in the control group. The

PCT, CRP and IL-6 levels of patients in both groups were significantly lower after treatment than before treatment, and the PCT, CRP and IL-6 levels of patients in the observation group were significantly lower than those in the control group. The above results suggest that Gegen Qinlian Decoction combined with a Chinese herbal hot package may inhibit the gastrointestinal mucous membrane infection-related pathogens, reduce PCT, CRP and IL-6 production, stop the spread of inflammatory factors, promote the timely recovery of inflammatory symptoms, and shorten the treatment time.

In conclusion, the clinical efficacy of Gegen Qinlian Decoction combined with Chinese herbal hot package in the treatment of AGE is remarkable, which can effectively improve the clinical symptoms of patients and reduce the inflammatory reaction, and is worthy of clinical promotion.

Acknowledgments

Not applicable.

Conflict interest

The authors declare that they have no conflict of interest.

References

1. Ali S, Maki C, Xie J, Lee BE, Dickinson J, MacDonald SE, Poonai N, Thull-Freedman J, Vanderkooi O, Rajagopal M, Sivakumar M, Chui L, Graham TAD, Nettel-Aguirre A, Svenson LW, Freedman SB; Alberta Provincial Pediatric EnTeric Infection TEam (APPETITE Team) and Pediatric Emergency Research Canada (PERC). Characterizing Pain in Children with AGE Who Present for Emergency Care. *J Pediatr*. 2021 Apr;231:102-109.e3. doi: 10.1016/j.jpeds.2020.12.029. Epub 2020 Dec 15. PMID: 33333114.
2. Vandesande H, Edman K, Rondahl E, Falkeborn T, Serrander L, Lindberg AM. Saffold virus infection in elderly people with AGE in Sweden. *J Med Virol*. 2021 Jun;93(6):3980-3984. doi: 10.1002/jmv.26452. Epub 2020 Oct 30. PMID: 32827319.
3. Fleckenstein JM, Matthew Kuhlmann F, Sheikh A. Acute Bacterial Gastroenteritis. *Gastroenterol Clin North Am*. 2021 Jun;50(2):283-304. doi: 10.1016/j.gtc.2021.02.002. Epub 2021 Apr 23. PMID: 34024442; PMCID: PMC8793005.
4. Adeyemi OO, Alabi AS, Adeyemi OA, Talabi OT, Abidakun OM, Joel IY, Stonehouse NJ. AGE and the usage pattern of antibiotics and traditional herbal medications for its management in a Nigerian community. *PLoS One*. 2021 Oct 4;16(10): e0257837. doi: 10.1371/journal.pone.0257837. PMID: 34607333; PMCID: PMC8490005.
5. Zhu K, Ye S X, Huang S. Efficacy of TCM evidence-based treatment combined with conventional Western medicine in the treatment of AGE and the effect on the level of inflammatory factors. *Liaoning Journal of Traditional Chinese Medicine*.2019,46(04):785-787.
6. Chen LH, Tang YP, Wang Q. Modern research progress of Gegen Qinlian Decoction. *Chinese herbal medicine*.2010,41(04):676-680.
7. Cai L. Clinical observation on the treatment of diarrhea-type irritable bowel syndrome (evidence of spleen and stomach weakness) with hot package[D]. Chengdu University of Traditional Chinese Medicine,2020.
8. Chen F. Clinical observation on the treatment of acute enteritis with Gegen Fuling decoction combined with physical therapy. *Sichuan Traditional Chinese Medicine*.2016,34(07):142-143.
9. Huicho L, Campos M, Rivera J, et al. Fecal screening tests in the approach to acute infectious diarrhea: a scientific overview. *Pediatr Infect Dis J* 1996;15:486Y94.
10. Wakefield CH, Barclay GR, Fearon KC, Goldie AS, et al. Proinflammatory mediator activity, endogenous antagonists and the systemic inflammatory response in intraabdominal sepsis. *Scottish Sepsis Intervention Group. Br J Surg*1998; 85:818–25.
11. Calandra T, Gerain J, Heumann D, Baumgartner JD, Glauser MP. High circulating levels of interleukin-6 in patients with septic shock: evolution during sepsis, prognostic value, and interplay with other cytokines. The Swiss–Dutch J5 Immunoglobulin Study Group. *Am J Med*. 1991; 91:23–9.
12. Le JM, Vilcek J. Interleukin 6: a multifunctional cytokine regulating immune reactions and the acute phase protein response. *Lab Invest*.1989;61:588–602.
13. Lubasch A, Lode H. The role of antibiotic therapy in infectious enteritis. *Internist*.2000;41:494–7.
14. Lin CH, Hsieh CC, Chen SJ, Wu TC, Chung RL, Tang RB. The diagnostic value of serum interleukins 6 and 8 in children with AGE. *J Pediatr Gastroenterol Nutr*. 2006 Jul;43(1):25-9. doi: 10.1097/01.mpg.0000235764.30743.5b. PMID: 16819373.
15. L. Joshi, M. Ponnana, R. Sivangala, L.K. Chelluri, P. Nallari, S. Penmetsa, V. Valluri, S. Gaddam, Evaluation of TNF-alpha, IL-10 and IL-6 Cytokine Production and Their Correlation with Genotype Variants amongst Tuberculosis Patients and Their Household Contacts, *PloS One* 10 (9) (2015) e0137727.
16. Borgnolo G, Barbone F, Guidobaldi G, Olivo G. CRP in viral and bacterial gastroenteritis in childhood. *Acta Paediatr*. 1996 Jun;85(6):670-4. doi: 10.1111/j.1651-2227.1996.tb14121.x. PMID: 8816201.
17. Marcus N, Mor M, Amir L, Mimouni M, Waisman Y. The quick-read CRP test for the prediction of bacterial gastroenteritis in the pediatric emergency department.

- Pediatr Emerg Care. 2007 Sep;23(9):634-7. doi: 10.1097/PEC.0b013e31814a6a52. PMID: 17876252.
18. Louw JJ, Toelen J, Proesmans M, Vermeulen F, Billen J, de Boeck K. Serum procalcitonin is not an early marker of pulmonary exacerbation in children with cystic fibrosis. *Eur J Pediatr*. 2012 Jan;171(1):139-42. doi: 10.1007/s00431-011-1502-x. Epub 2011 Jun 1. PMID: 21630003.
 19. Thia KT, Chan ES, Ling KL, Ng WY, Jacob E, Ooi CJ. Role of procalcitonin in infectious gastroenteritis and inflammatory bowel disease. *Dig Dis Sci*. 2008 Nov;53(11):2960-8. doi: 10.1007/s10620-008-0254-6. Epub 2008 Apr 16. PMID: 18415679.
 20. Ana Belen. Use of procalcitonin as diagnostic marker in AGE. <https://dx.doi.org/10.4067/S0370-41062014000200004>.
 21. Antoniazzi S, Cattaneo D, Perrone V, Carnovale C, Cherubini S, Mugolino MC, Clementi F, Zuccotti G, Clementi E, Radice S. Inflammation and neurological adverse drugs reactions: a case of lasting impaired consciousness after oxatomide administration in a patient with gastroenteritis. *Ital J Pediatr*. 2012 Mar 30;38(1):11. doi: 10.1186/1824-7288-38-11. PMID: 22464080; PMCID: PMC3337248.
 22. Antiemetic agents are contraindicated in children with AGE. *Ned Tijdschr Geneesk*. 2005 Jun 25;149(26):1437. Dutch. PMID: 16010952.
 23. Ganjali, S., Khajeh, H., Gholami, Z., Jomehghasemabadi, Z., Fazeli-Nasab, B. Evaluation of Dormancy Failure *Datura stramonium* Plant Seeds under the Influence of Different Treatments. *Agrotech Ind Crops* 2022; 2(1): 32-41. doi: 10.22126/atic.2022.7656.1049
 24. Ghamarnia H, Mousabeygi F, Rezvani S. Water Requirement, Crop Coefficients of Peppermint (*Mentha piperita* L.) and Realizing of SIMDualKc Model. *Agrotech Ind Crops* 2021; 1(3): 110-121. doi: 10.22126/atic.2021.6791.1019
 25. Aryafar S, Sirousmehr A, Najafi S. The Impact of Compost on Seed Yield and Essential Oil of Black Cumin under Drought Stress Conditions. *Agrotech Ind Crops* 2021; 1(3): 139-148. doi: 10.22126/atic.2021.7184.1026
 26. Almasi F. Organic Fertilizer Effects on Morphological and Biochemical Traits and Yield in Coriander (*Coriandrum sativum* L.) as an Industrial and Medicinal Plant. *Agrotech Ind Crops* 2021; 1(1): 19-23. doi: 10.22126/etic.2021.6476.1011.
 27. Shaafi B, Mosavi S, Abdollahi M, Sarikhani H. The Optimized Protocols for Production, Adaptation and Keeping of the Produced Artificial Seeds from Encapsulated Lateral Buds in *Stevia rebaudiana* (Bertoni). *Agrotech Ind Crops* 2021; 1(1): 24-35. doi: 10.22126/etic.2021.6246.1004
 28. Wu L, Peng L, Chen R. Progress in clinical application and experimental research of *Gegen Qinlian* Decoction. *Henan Traditional Chinese Medicine*, 2021, 41 (4): 527-531.