European Review for Medical and Pharmacological Sciences 2022; 26: 5814-5820

Effect of pharmaceutical care on the treatment of community-acquired pneumonia in the elderly: a case report

Y. JIANG, Z.-Q. DU, H.-H. ZHU, Q. WANG

The Affiliated Wuxi Mental Health Center of Jiangnan University, Wuxi Tongren Rehabilitation Hospital, Wuxi, Jiangsu, China

Ying Jiang and Zhiqiang Du contributed equally to this work

Abstract. – OBJECTIVE: Elderly patients with community-acquired pneumonia (CAP) have more comorbidities, decreased organ function, and weakened immune function, which can easily lead to various adverse reactionsduring anti-infection treatment. Comprehensive geriatric assessment is a commonly used method to optimize the management of the clinical treatment of the elderly, of which the clinical pharmacists are the core member. However, few studies have focused on the participation of relevant clinical pharmacists of comprehensive geriatric assessment (CGA) of elderly CAP patients.

CASE PRESENTATION: A case where the clinical pharmacist participated in the entire process of medical treatment of an elderly patient with CAP. From the first day of admission to the hospital, anti-infective drugs were selected based on the condition combined with the distribution and drug-resistance of common local pathogens, paying attention to the changes of various indicators during treatment, the drug dose was adjusted in time, and targeted anticoagulation, cardiotonic, diuretic, potassium supplementation, intestinal flora regulation and anti-fungal treatment were carried out, as well as the prevention and treatment of antibiotic-related diarrhea. After 24 days of hospitalization, the patient was in a stable condition after treatment and was discharged from the hospital.

CONCLUSIONS: The participation of clinical pharmacists in CGA had positive significance for the clinical treatment of elderly CAP, and it was worthy of further improvement and clinical promotion.

Key Words:

Community-acquired pneumonia in the elderly, Clinical pharmacist, Comprehensive geriatric assessment, Pharmaceutical care, Case report.

Abbreviations

CAP: Community-acquired pneumonia; CGA: Comprehensive geriatric assessment; Ccr: Creatinine clearance rate.

Introduction

As a relatively common respiratory system infectious disease, community-acquired pneumonia (CAP) refers to the infection of lung parenchyma outside the hospital, which is caused by a variety of microbial infections, including bacteria, viruses, chlamydia and mycoplasma. Specific pathogenic bacteria and drug resistance vary in different regions and change continuously over time[1]. The main clinical symptoms of the patients are fever, cough, purulent spu

tum, hemoptysis, chest pain and so on, which could be treated through anti-infective therapy combined with symptomatic treatment such as auxiliary oxygen, atomization, and phlegm reduction[2]. After treatment, the prognosis is related to the type of pathogenic bacteria and whether it is actively treated.

Community-acquired pneumonia in the elderly (elderly CAP) is generally defined as age ≥65 years[3]. *Streptococcus pneumoniae* remains the main pathogen of elderly CAP. But for elderly CAP patients with underlying diseases, it is necessary to consider the possibility of enterobacteria infection, and further evaluate the risk of being infected by extended-spectrum β-lactamase bacteria. Clinically, piperacillin, tazobactam, cefoperazone and sulbactam or *carbapenems* could be empirically selected for the treatment of elderly CAP[4,5]. However, due to the decline of organ function in the elderly, organ function needs to be monitored during treatment in order to choose the appropriate treatment according to the liver and kidney function.

Comprehensive geriatric assessment (CGA) is one of the most popular assessment tools abroad. It can improve or maintain the quality of life of the elderly to the greatest extent through the appraisal process of multiple perspectives, such as

Corresponding Authors: Haohao Zhu, MD; e-mail: zhuhaohao233@163.com; Qi Wang, MD; e-mail mhc1037@163.com

geriatrics, psychology and function. Researchers have conducted long-term CGA projects to optimize the clinical treatment management of elderly patients[6,7], which proved that CGA can promote the stability of patients' body functions, reduce the types of medications, shorten the length of hospital stay, and reduce the mortality rate. Studies[8,9] have reported that CGA can avoid undertreatment and optimize the treatment plans. With the emergence of multiple medications among elderly patients in recent years, there is an urgent need to fully implement the CGA method to formulate rational medication regimens for elderly patients, and clinical pharmacists are the core members of the CGA team who adjust multiple medications and optimize medication regimens. This article was the treatment process of an elderly CAP that the author participated in the consultation, which showed the importance of clinical pharmacists participating in the management of multiple medications in the CGA team through pharmacy practice to ensure safe, reasonable and effective medication for the elderly.

Case Presentation

The patient was a 70-year-old male, 170 cm, and 60 kg. The patient was admitted to the hospital with "cough, sputum, and chest tightness for 20 days". The patient developed cough and expectoration after being cold 20 days ago, mainly white sputum, a small amount of yellow sputum, approximately 20 mL/d, no sputum blood, no chest pain, no fever, mild chest tightness, which was more obvious after exercise. Before being admitted to the hospital, oral administration antibacterial and cough medicines (specifically unknown) were applied at home for more than 1 week; however, the symptoms had not improved, and the sputum was hard to cough up, accompanied by increased chest tightness. In the nearly 3 days, the patient was mainly lying in bed with a high pillow at night. During the course of the disease, the patient had mild anorexia and fatigue, no night sweats, no abdominal pain and diarrhea, normal bowel movements, and no significant weight loss.

Physical examination: T 37°C, P 68 times/min, and BP 168/98 mmHg. Consciousness, normal spirit, no swelling on face, soft neck, middle trachea, small thyroid gland, thick breath sounds in both lungs, a little moist rale can be heard in the right lower lung, territories not, no murmur, soft abdomen, no tenderness, rebound pain, liver, spleen and ribs were not reached, mobile dullness (-). There was no percussion pain in the kidney area, and no edema in both lower limbs. Auxiliary examination: SpO_2: 91% (without oxygen inhalation); chest radiograph showed pneumonia in the lower right. Admission diagnosis: bacterial pneumonia, coronary atherosclerotic heart disease, arrhythmia, old anterior wall myocardial infarction, cardiac insufficiency.

Therapy Process

Considering the repeated use of antibacterial drugs, the patient was administered cefoperazone and sulbactam sodium (2 g, intravenous drip, every 12 h) for anti-infective treatment, and ambroxol hydrochloride (30 mg, intravenous injection, 2 times a day) for expectorant treatment after admission.

On the second day of admission, the blood routine showed elevated neutrophils and elevated D-dimer. Low-molecular-weight heparin calcium (5000 IU, subcutaneous injection, once a day) was given for anticoagulant therapy, and pantoprazole sodium for injection (40 mg, intravenous injection, once a day) was given to sulphuric acid.

On the third day, the creatinine clearance rate (Ccr) of the patient was 21.6 mL/min. The clinical pharmacist suggested that the injection of cefoperazone and sulbactam sodium should be adjusted to 1 g, intravenous drip with once every 12 hours. Due to the patients with the complication of cardiac insufficiency, digoxin tablets (0.125 mg, orally, once a day) were added to strengthen the heart.

On the 12th day, the symptoms of cough and sputum improved significantly, and antibacterial drugs were discontinued after a full course of treatment. However, the chest tightness worsened at night. Considering the cause of cardiac insufficiency, torsemide (20 mg, intravenous injection, once a day) was ordered to strengthen diuresis to reduce cardiac load. Reexamination of blood electrolytes reveals no abnormalities, but the blood potassium was at a low level. This indicated that lower intake and repeated diuresis tended aggravate electrolyte imbalance, therefore, potassium chloride sustained-release tablets (1 g, orally, 2 times a day) were administered for potassium supplementation. Acid-fast bacilli, bacteria and fungi were not detected in sputum smears, and the results of sputum bacteria and fungal cultures were negative.

On the 14th day, the symptoms of heart failure were relieved, and torsemide was discontinued; the patient occasionally experienced repeated abdominal discomfort and poor appetite.

On the 20th day, because of more bowel movements, the patient was treated with a combination of *clostridium butyricum* and *bifidobacterium* powder (live, 0.84 g, orally, 3 times a day) and montmorillonite powder (3 g, orally, 3 times a day) for symptomatic treatment. According to the symptoms of cough with white sticky sputum, which was not easy to cough up with wire drawing, and considering the medication history of broad-spectrum antibiotics lead to the low immunity, the clinical pharmacist concluded that it may be caused by fungal infection. The fluconazole injection (400 mg on the first day, 200 mg thereafter, intravenous drip, once a day) was recommended for antifungal treatment.

On the 21st day, the patient developed abdominal distension and was treated symptomatically with domperidone to promote gastrointestinal motility.

On the 22nd day, the stool bacterial smear showed that the G+ cocci grew predominantly. Considering antibiotic-related diarrhea could not be ruled out, metronidazole tablets (0.2 g, orally, 3 times a day) were recommended by clinical pharmacist.

On the 24th day, the patient was stable, without chest tightness, asthma, chest pain, and abdominal pain and diarrhea, and was discharged from the hospital. Discharge diagnosis: bacterial pneumonia, coronary atherosclerotic heart disease, arrhythmia, old anterior myocardial infarction, cardiac insufficiency. Discharge medication: digoxin tablets (0.125 mg, orally, once a day), aspirin tablets (100 mg, orally, once a day), metronidazole tablets (0.2 g, orally, 3 times a day). Besides, the patient was asked to take rest, avoid colds, strengthen nutritional support, low-salt and low-fat diet, and follow up regularly.

With the established individual pharmaceutical care, the patient took the medication regularly and quantitatively throughout the treatment process, which improved the medication compliance, and avoided obvious adverse drug reactions.

The patient hoped us to continuously improve the individual pharmaceutical care to help more and more patients in the near future.

Discussion

Elderly CAP patients have certain particularities, such as many comorbidities, with systemic damage (such as cognitive impairment, metabolic disorders, kidney damage, etc.), accompanied by inhalation factors. A sufficient assessment of pathogenic susceptibility is helpful for the selection of anti-infection treatment options. The pharmaceutical care offered by clinical pharmacist is a comprehensive clinical medication service provided by technical personnel with specialized pharmacy knowledge to patients, the main purpose of which is to ensure medication safety and therapeutic effect of patients during treatment.

During the treatment process, pharmacists participate in clinical treatment[10], are participants, consultants, researchers and supervisors of clinical medication, and have the right and obligation to supervise, guide, evaluate and intervene in rational medication use in the clinic. In recent years, there have been relevant research reports at home and abroad on the clinical application of pharmaceutical intervention. These studies have shown that the active participation of clinical pharmacists in the management of drug regimens has clear significance for the rational use of antibiotics[11-15].

Data from prospective studies such as Marquis showed that clinical pharmacists involved in pre-drug consultation and clinical drug regimen formulation, compared with those without clinical pharmacist intervention, patients had a shorter course of treatment and a lower incidence of adverse renal toxicity[10]. However, the application of clinical pharmacists in elderly patients with CAP is less studied.

In this study, clinical pharmacists analyzed and evaluated the case and related drugs by referring to the drug instructions and relevant domestic and foreign guidelines, mainly from hospital management indicators, medication indications (indications, preventive medication indications, prescriptions) Physician authority, indications of combined medication), medication process (administration route, medication timing, vehicle selection, medication dose, medication frequency, medication course, infusion time, interaction, etc.), medication outcome (clinical symptoms, vital signs, Laboratory examinations, etiological examinations, and drug sensitivity tests) were helpful to timely identify problems in clinical use and intervene, and analyze the rationality before and after intervention, so as to promote rational clinical use.

The Choice of Anti-infective Drugs

Initial choice of anti-infective drugs: The patient was clearly diagnosed with CAP (increased cough and sputum, a little wet rale on the right lower lung,

chest radiograph showing right lower pneumonia), and its common pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, Respiratory viruses, etc. Recommended programs: ① penicillins + β-lactamase inhibitors; ② cephalosporins (cefuroxime, ceftriaxone, cefotaxime sodium, etc.) + macrolides (azithromycin, etc.); ③ respiratory quinolones (levofloxacin, moxifloxacin, etc.)[3]. Considering the risk factors (such as age > 65 years, application of β-lactam antibiotics in the past 3 months, etc.), the patient might have been infected with drug-resistant streptococcus pneumoniae, and had a high risk of drug-resistant G-bacillus infection. Cefoperazone and sulbactam belong to the third-generation cephalosporin and β-lactamase inhibitor, respectively, which have obvious synergistic antibacterial effects on G-bacteria and various drug-resistant bacteria. Therefore, it was reasonable to choose cefoperazone and sulbactam sodium for injection (2 g, intravenous drip, once every 12 hours) for anti-infective treatment. Considering that the Ccr of the patient was 21.6 mL/min on the third day of admission, according to the "National Antimicrobial Therapy Guidelines. 2nd Edition"[16], the dose should be adjusted for patients with renal insufficiency: 15<Ccr<30 ml/min. Therefore, the dosage of cefoperazone and sulbactam sodium for injection was recommended to adjust (1 g, intravenous drip, once every 12 hours), the clinician adopted the suggestion and revised the treatment plan to achieve better outcomes.

Drug adjustment after the patient's condition changed: 12 days after the initial anti-infective treatment, the drugs were stopped after the condition of the patient improved. One week later, the patient developed clinical manifestations of suspected fungal infection: a small amount of coughing with white sticky sputum, not easy to cough up with stringing. Consider that the patient had the medication history of broad-spectrum antibacterial drugs, which weakened his immunity, and combined with the sputum was thick and difficult to cough up, there was a possibility of fungal infection. Candida is the most common pathogen causing invasive fungal infections, especially pulmonary fungal diseases[17]. Fluconazole is the first-choice for anti-candida with the usual dose specified in its instructions being 400 mg on the first day and 200 mg/d afterwards. If the Ccr ≤50 mL/min, 50% dose is recommended. Besides, the "Candida Diagnosis and Treatment: Expert Consensus" recommends fluconazole 800 mg on the first day and 400 mg per day thereafter[18]. Considering that the Ccr of the patient was 21.6 mL/min, the fluconazole dose must be halved. Therefore, in order to reach the steady-state blood drug concentration as soon as possible to exert effective antifungal effects, it was recommended to adopt a regimen of 400 mg on the first day and 200 mg/d afterwards, and clinicians adopted the recommendation with the disappearance of the clinical symptoms of the patient.

Prevention and Treatment of Related Diarrhea Caused by Anti-Infective Drugs

The widespread application of antibacterial drugs has saved the lives of the patient with infectious diseases, however, adverse reactions related to anti-infective therapy have also increased. Except for vancomycin, almost all antibacterial drugs have the potential to cause antibiotic-related diarrhea, with an incidence of 5-20%[19,20]. Studies[21,22] have found that the independent risk factors for antibiotic-related diarrhea are: age <14 years old and ≥60 years old, various types of antibiotics, long treatment time, high APACHE II score, fasting, etc. Elderly patients with declined organ function, weakened immune function, and a variety of underlying diseases, are high-risk group of intestinal flora imbalance. Therefore, when elderly patients must use antibacterial drugs, the medication time should be as short as possible, and the medication should be changed or stopped in time, or the intestinal flora regulator should be applied preventively.

If patients with antibiotic-related diarrhea still require anti-inflammatory treatment, antibacterial drugs with a low incidence of antibiotic-related diarrhea should be selected, such as metronidazole (200 mg, 3 times a day) or vancomycin (125 mg, 4 times a day). In order to prevent the emergence of vancomycin-resistant strains, the American Society of Infectious Diseases, the American Gastroenterology Society and the American Epidemiological Society recommend metronidazole as the first choice[23]. In addition, lactic acid bacteria, *bifidobacteria*, *enterococci* and other microbial preparations could replenish the normal intestinal flora, regulate the imbalance of the intestinal flora, and rebuild the intestinal biological barrier through biological antagonism (defense infection), adherence to colonization and biological barriers, nutritional competition, immune regulation, biological oxygen deprivation, acid production inhibition, and possessive effects. Therefore, those microbial preparations have the potential to prevent and treat antibiotic-related diarrhea[24-27].

In the manuscript, multiple risk factors for antibiotic-related diarrhea could be observed at the patient (such as age ≥ 60 years old, various

types of antibiotics, long-term use of antibiotic, etc.). After treatment with broad-spectrum antimicrobial drugs, the increased number of stools and the predominantly growth of G+ cocci suggested an imbalance in the intestinal flora of the patient. Considering that antibiotic-related diarrhea cannot be ruled out, it was recommended to add metronidazole tablets (0.2 g, orally, 3 times a day) for anti-anaerobic treatment. Simultaneously, the intestinal flora was adjusted by the combination of live clostridium butyricum (0.84 g, orally, 3 times a day), and montmorillonite powder (3 g, orally, 3 times a day) for antidiarrheal treatment. The clinician adopted the recommendations for the better treatment of the patient. However, limitations could be found in our study, such as the small sample size, the adjustment of medication mainly based on the experience of the pharmacist.

Conclusions

Elderly CAP patients are often accompanied by blood electrolyte disorders and abnormal liver and kidney functions. In principle, attention should be paid to the treatment of pneumonia and various abnormal organs. At the same time, due to the physiological development factors and the influence of the disease, the liver and kidney functions of the patients will be decreased. The frequency and dosage of the corresponding treatment drugs should be adjusted in time. Therefore, it is necessary to comprehensively evaluate the liver and kidney functions of elderly CAP to adjust the dosing regimen to avoid adverse reactions.

For anti-infective treatment, pathogen culture and drug susceptibility results should be the accurate basis for clinical selection of antimicrobial drugs, but the initial empirical treatment of CAP patients is still urgently needed. Antibiotics should be selected according to the personal condition, combined with the distribution and drug-resistance of local common pathogens. After 3 days of empirical treatment, the clinician should determine to adjust the medication or continue the original treatment according to the re-evaluated condition of the patient, as well as comprehensive consideration of the disease development and drug sensitivity results. After hospitalized for 24 days under the pharmaceutical care, the patient reported here was discharged from the hospital with stable condition. The clinical pharmacist participated in the formulation of treatment plans and follow-up for pharmaceutical monitoring throughout the drug treatment, which promoted the safety and rational use of drugs for elderly patients and helped them avoid adverse reactions.

Competing Interests

The authors declare that they have no conflict of interest.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Wuxi Mental Health Centre, with the grant number of WXMH-CIRB2020LLky042. Written informed consent was obtained from the patient. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for Publication

The patient understood the report, and signed informed consents.

Availability of Data and Materials

The dataset generated during and analysed during the current study are available from the corresponding author on reasonable request.

Funding

The work is supported by the National Natural Science Foundation of China (No. 8210131157), Science and Technology Development Foundation of Nanjing Medical University (No. NMUB2020296 and NMUB2020297), Wuxi Municipal Health Commission (No. Q202101 and ZH202110), Wuxi Taihu Talent Project (No. WXTTP2020008 and WXTTP2021) and a grant from Jiangsu Research Hospital Association for Precision Medication (JY202105).

Authors' Contributions

Conceptualization, Du. Z.Q. and Jiang. Y.; methodology, Du. Z.Q. and Wang. Q.; writing – original draft preparation, Zhu. H. H.; writing – review and editing, Zhu. H.H. All authors have read and agreed to the published version of the manuscript.

Acknowledgements

Not applicable.

References

1) Lanks CW, Musani AI, Hsia DW. Community-acquired Pneumonia and Hospital-acquired Pneumonia. Med Clin North Am 2019; 103: 487-501.

2) Olson G, Davis AM. Diagnosis and Treatment of Adults With Community-Acquired Pneumonia. JAMA 2020; 323: 885-886.
3) Chinese Society of Respiratory Diseases. Guidelines for the diagnosis and treatment of community-acquired pneumonia in Chinese adults. Chin J Tuber Resp Med 2016; 39: 1-27.
4) Carugati M, Aliberti S, Sotgiu G, Blasi F, Gori A, Menendez R, Encheva M, Gallego M, Leuschner P, Ruiz-Buitrago S, Battaglia S, Fantini R, Pascual-Guardia S, Marin-Corral J, Restrepo MI; GLIMP Collaborators. Bacterial etiology of community-acquired pneumonia in immunocompetent hospitalized patients and appropriateness of empirical treatment recommendations: an international point-prevalence study. Eur J Clin Microbiol Infect Dis 2020; 39: 1513-1525.
5) Al-Tawfiq JA, Momattin H, Hinedi K. Empiric Antibiotic Therapy in the Treatment of Community-acquired Pneumonia in a General Hospital in Saudi Arabia. J Glob Infect Dis 2019; 11: 69-72.
6) Pilotto A, Cella A, Pilotto A, Daragjati J, Veronese N, Musacchio C, Mello AM, Logroscino G, Padovani A, Prete C, Panza F. Three Decades of Comprehensive Geriatric Assessment: Evidence Coming From Different Healthcare Settings and Specific Clinical Conditions. J Am Med Dir Assoc 2017; 18: 192.e1-192.e11.
7) Parker SG, McCue P, Phelps K, McCleod A, Arora S, Nockels K, Kennedy S, Roberts H, Conroy S. What is Comprehensive Geriatric Assessment (CGA)? An umbrella review. Age Ageing 2018; 47: 149-155.
8) Partridge JS, Harari D, Martin FC, Peacock JL, Bell R, Mohammed A, Dhesi JK. Randomized clinical trial of comprehensive geriatric assessment and optimization in vascular surgery. Br J Surg 2017; 104: 679-687.
9) Fusco D, Ferrini A, Pasqualetti G, Giannotti C, Cesari M, Laudisio A, Ballestrero A, Scabini S, Odetti PR, Colloca GF, Monzani F, Nencioni A, Antonelli Incalzi R, Monacelli F; Oncogeriatrics Group of the Italian Society of Gerontology, Geriatrics. Comprehensive geriatric assessment in older adults with cancer: Recommendations by the Italian Society of Geriatrics and Gerontology (SIGG). Eur J Clin Invest 2021; 51: e13347.
10) Marquis KA, DeGrado JR, Labonville S, Kubiak DW, Szumita PM. Evaluation of a Pharmacist-Directed Vancomycin Dosing and Monitoring Pilot Program at a Tertiary Academic Medical Center. Ann Pharmacother 2015; 49: 1009-1014.
11) Yoo R, So H, Seo E, Kim M, Lee J. Impact of initial vancomycin pharmacokinetic/pharmacodynamic parameters on the clinical and microbiological outcomes of methicillin-resistant Staphylococcus aureus bacteremia in children. PLoS One 2021;16: e0247714.
12) Nakashima T, Koido K, Baba H, Otsuka R, Okinaka K, Sano T, Nishigaki R, Hashimoto H, Otsuka T, Esaki M, Terakado H. Contribution of pharmacists with expertise in infectious diseases to appropriate individualized vancomycin dosing. Pharmazie 2018; 73: 422-424.
13) Okada N, Fushitani S, Azuma M, Nakamura S, Nakamura T, Teraoka K, Watanabe H, Abe M, Kawazoe K, Ishizawa K. Clinical Evaluation of Pharmacist Interventions in Patients Treated with Anti-methicillin-Resistant Staphylococcus aureus Agents in a Hematological Ward. Biol Pharm Bull 2016; 39: 295-300.
14) Yamada M, Matsumura C, Jimaru Y, Ueno R, Takahashi K, Yano Y. Effect of Continuous Pharmacist Interventions on Pain Control and Side Effect Management in Outpatients with Cancer Receiving Opioid Treatments. Biol Pharm Bull 2018;41: 858-863.
15) Xu G, Chen E, Mao E, Che Z, He J. Research of optimal dosing regimens and therapeutic drug monitoring for vancomycin by clinical pharmacists: analysis of 7-year data. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2018; 30: 640-645.
16) He L X, Xiao Y H, Lu Q. National Antimicrobial Therapy Guidelines. 2nd edition. Beijing: People's Medical Publishing House 2017: 247.
17) Lao M, Li C, Li J, Chen D, Ding M, Gong Y. Opportunistic invasive fungal disease in patients with type 2 diabetes mellitus from Southern China: Clinical features and associated factors. J Diabetes Investig 2020; 11: 731-744.
18) Chinese Medical Association. Diagnosis and treatment of candidiasis: expert consensus. Chin J Infect Chemo 2011; 11: 81-95.
19) Silverman MA, Konnikova L, Gerber JS. Impact of Antibiotics on Necrotizing Enterocolitis and Antibiotic-Associated Diarrhea. Gastroenterol Clin North Am 2017; 46: 61-76.
20) Lv W, Liu C, Ye C, Sun J, Tan X, Zhang C, Qu Q, Shi D, Guo S. Structural modulation of gut microbiota during alleviation of antibiotic-associated diarrhea with herbal formula. Int J Biol Macromol 2017; 105: 1622-1629.
21) Zhou H, Xu Q, Liu Y, Guo LT. Risk factors, incidence, and morbidity associated with antibiotic-associated diarrhea in intensive care unit patients receiving antibiotic monotherapy. World J Clin Cases 2020; 8: 1908-1915.
22) Takedani Y, Nakamura T, Fukiwake N, Imada T, Mashino J, Morimoto T. Clinical characteristics and factors related to antibiotic-associated diarrhea in elderly patients with pneumonia: a retrospective cohort study. BMC Geriatr 2021; 21: 317.
23) Periman P. Antibiotic-associated diarrhea. N Engl J Med 2002; 347: 145.
24) Wu J, Gan T, Zhang Y, Xia G, Deng S, Lv X, Zhang B, Lv B. The prophylactic effects of BIFICO on the antibiotic-induced gut dysbiosis and gut microbiota. Gut Pathog 2020; 12: 41.
25) Liao W, Chen C, Wen T, Zhao Q. Probiotics for the Prevention of Antibiotic-associated Diarrhea in Adults: A Meta-Analysis of Randomized Placebo-Controlled Trials. J Clin Gastroenterol 2021; 55: 469-480.
26) Khademian M, Kiani MA, Jafari SA, Ahanchian H, Sedghi N, Behmanesh F, Khakshour A, Kianifar H.

Probiotic or Conventional Yogurt for Treating Antibiotic-associated Diarrhea: A Clinical Trial Study. Int J Pediatr 2018; 6: 7405-7412.

27) Blaabjerg S, Artzi DM, Aabenhus R. Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Outpatients-A Systematic Review and Meta-Analysis. Antibiotics (Basel) 2017; 6: 21.