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Antibiotic-associated Diarrhea in Elderly Patients with Community-acquired Pneumonia: The Impact of Probiotics on Prevention and Treatment

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ABSTRACT

Background: Community-acquired pneumonia is common in the elderly because of decreased immune function. Using broad-spectrum can lead to gut dysbiosis and antibiotic-associated diarrhea (AAD). Co-administration of probiotics during antibiotic treatment is a reasonable way to prevent AAD. The clinical application of probiotics is mainly related to improving gastrointestinal symptoms; they reduce the overgrowth of potentially pathogenic microorganisms, improve gut mucosal barrier function, reduce bacterial translocation, and reduce toll-like receptor-mediated up-regulation of immune function.

Objectives: This study aimed to investigate the clinical value of probiotic treatment in elderly patients with pneumonia.

Methods: We studied 85 elderly patients diagnosed with community-acquired pneumonia. The patients were divided into the probiotic and control groups and treated according to the pneumonia treatment guidelines. In the probiotic group, Lacto-G forte (*Lactobacillus acidophilus, Bifidobacterium longum, Bifidobacterium bifidum, Bifidobacterium lactis*) was used, while patients of the control group received a placebo. Frequency of ADD, length of hospital stays, duration of antimicrobial therapy, stool qualitative and quantitative characteristics, days till stool normalization, and safety profile were registered during the study.

Results: Antibiotic-associated diarrhea in the Lacto-G Forte group was 12 cases - 27.9%, i.e., experimental event rate (EER)=0.279, and in the control group, was 26 cases - 61.9%, i.e., control event rate (CER) = 0.619. In the Lacto-G Forte group, compared to the placebo group, there was a 55% reduction in relative risk, or relative risk reduction (RRR) = 0.55, and a 34.0% reduction in absolute risk, or absolute risk reduction (ARR) = 0.34. NNT analysis of data from the probiotic and placebo groups revealed that the number needed to treat is 3. The average time to resolve diarrhea in the Lacto-G Forte group was 1.38±0.62 days, and in the placebo group - 2.37±0.84 days.

Conclusions: Lacto-G Forte supplementation in elderly patients with community-acquired pneumonia reduces the risk of developing antibiotic-associated diarrhea and can resolve it quickly.

Keywords: Antibiotic-associated diarrhea (AAD); community-acquired pneumonia; elderly patients; gut dysbiosis; Lacto-G Forte; probiotics.

BACKGROUND

Community-acquired pneumonia is common in the elderly, requiring appropriate antibacterial therapy, a risk of gut dysbiosis, and antibiotic-associated diarrhea (AAD). Once AAD occurs, it results in additional treatment, extended hospital stays, and extra costs.[1,2] Co-administration of probiotics during antibiotic treatment is a reasonable way to prevent AAD.[3]

Probiotics are live, non-pathogenic microorganisms that reduce bacterial translocation by activating mucosal immunity, and their use benefits human health. Most mechanisms by which probiotics exhibit their effects are unknown, but the primary is the stimulation of immunomodulatory cells.[4,5] Probiotics increase short-chain fatty acids (SCFA) and suppress systemic inflammatory response by stabilizing the gut microbiota.[4,6] The gut microbiota influences T and B cells and could be related to immune and inflammatory diseases.[7]

There is an increased interest in probiotic interventions and their effectiveness in preventing AAD. There is good evidence that probiotics can prevent AAD in systemic antibiotic patients.[8-10] The clinical application of probiotics is mainly related to improving gastrointestinal symptoms.[11] They reduce the overgrowth of potentially pathogenic microorganisms, improve gut mucosal barrier function, reduce bacterial translocation, and toll-like receptor-mediated up-regulation of immune function.[12,13]

In this controlled study, we aimed to investigate the effectiveness and safety of Lacto-G Forte for the prevention and treatment of antibiotic-associated diarrhea in elderly patients with community-acquired pneumonia.

METHODS

We studied 85 elderly patients diagnosed with pneumonia admitted to the Internal Medicine Department of TSMU and

Ingorokva High Medical Technology University Clinic from January to October 2022. There were 58 males and 27 females, with an average age of 72.9±5.3 years. The patients were divided into the probiotic and control groups. There were 43 patients: 28 males and 15 females in the probiotic group, with an average age of 74.3±5.05 years, and 42 patients: 30 males and 12 females – in the control group, with an average age of 73±5.2 years. There was no significant difference in gender, age, and other baseline characteristics between these groups. All patients were informed of the study and signed an informed consent form.

The inclusion criteria were:

- Hospitalized patients of both genders aged ≥60 years receiving oral or parenteral antimicrobial therapy because of community-acquired pneumonia;
- Duration of antibiotic treatment ≤48 hours.

The exclusion criteria were:

- Diarrhea at the moment of hospitalization or within the last week before hospitalization;
- Chronic disease with recurrent diarrhea;
- Antimicrobial therapy taken/ongoing within the last 4 weeks before hospitalization;
- Regular intake of probiotics/eubiotics/symbiotics;
- Lactose intolerance;
- Taking laxatives.

Patients in both groups were treated according to the community-acquired pneumonia treatment guidelines. The probiotic group was additionally treated with Lacto-G forte (*Lactobacillus acidophilus, Bifidobacterium longum, Bifidobacterium bifidum, Bifidobacterium lactis*), while patients of the control group received a placebo along antimicrobial therapy. Each patient took three capsules of probiotic or placebo once a day in the morning before a meal during the active antibiotic treatment period (maximum 10 days). The last dose was administered on the previous day of antibiotic treatment. After the end of treatment, patients were followed up for 4 weeks.

Baseline data (gender, age, body mass index, alcohol consumption and smoking status, number of antibiotics, degree of antibiotic-associated diarrhea) were collected from patients.

The following laboratory tests were performed:

- Complete blood count (CBC);
- Determination of serum electrolyte concentrations;
- Quantitative determination of C-reactive protein (CRP);
- Determination of serum thyroid-stimulating hormone (TSH) concentration;
- Determination of serum free thyroxine (FT4) concentration;
- Coprological analysis for *Clostridioides difficile* toxins:
  - Glutamate dehydrogenase (GDH) antigen test;
  - Toxin A and B test;
  - If necessary (GDH-positive/toxin-negative or GDH-negative/toxin-positive): nucleic acid amplification test (NAAT);

During the study, the frequency of ADD, length of hospital stays, duration of antimicrobial therapy, stool qualitative and quantitative characteristics, days till stool normalization, and safety profile were registered.

Statistical analysis

Measurement data are expressed as mean ± standard deviation. The chi-square test was used to calculate P values for qualitative data. The quantitative data conforming to normal distribution were analyzed using an independent sample t-test, and $p < 0.05$ was considered statistically significant. An intention-to-treat (ITT) analysis of the results was provided. Number Need to Treat (NNT) analysis assessed the preventive efficacy of antibiotic-associated diarrhea.

RESULTS

Table 1 provides baseline and clinical information on patients.

TABLE 1. Baseline characteristics of study patients

	Group A (Lacto-G Forte)	Group B (Placebo)	p-value
Age, years	74.3±5.05	73±5.21	0.56
Gender, male/female	28/15	30/12	0.67
Smokers/nonsmokers, %	23/77	21/79	0.52
Body mass index, kg/m^2	27.7±4.4	28.0±4.3	0.91
Comorbidity	1.4±0.9	1.3±1.0	0.51
K, mmol/L	3.62±0.39	3.60±0.42	0.72
Na, mmol/L	134.0±9.40	134.3±7.36	0.61
WBC, x10^9/L	11.14±9.13	10.96±3.41	0.62
CRP, mg/L	47.73±33.47	52.40±29.50	0.41
TSH, mIU/l	1.89±0.84	1.90±0.72	0.72
FT$_4$, ng/dl	1.26±0.23	1.31±0.22	0.41

Abbreviations: CRP, C reactive protein; FT4, free thyroxine; K, potassium; Na, sodium; TSH, thyroid-stimulating hormone; WBC, leucocytes.

There was no significant difference in age, gender, smoking status, BMI, or comorbidities between groups. Also, there were no significant differences in the laboratory test results before treatment (Tab.1).

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We analyzed the clinical outcomes of the patient after the treatment. There was no significant difference in the number of days of fever: probiotic group 5.58±1.2 and 5.67± 1.3 in the control group, and length of stay: 9.53±1.32 days in the probiotic group and 9.76±1.34 in the control group (Tab.2).

TABLE 2. Clinical characteristics of study patients after treatment

	Group A (Lacto-G Forte)	Group B (Placebo)	p-value
Length of hospitalization	9.53±1.32	9.76±1.34	0.62
Duration of hyperthermia	5.58±1.2	5.67±1.3	0.51
Antibiotic-associated diarrhea	12	26	0.84
Time to resolution of diarrhea	1.38±0.62	2.37±0.84	0.70

A study of the incidence of diarrhea showed that the incidence of antibiotic-associated diarrhea in the Lacto-G Forte group was 12 cases - 27.9%, i.e., experimental event rate (EER)=0.279 and in the control group, was 26 cases - 61.9%, i.e., control event rate (CER)=0.619. In the Lacto-G Forte group, compared to the placebo group, there was a 55% reduction in relative risk, or relative risk reduction (RRR)=0.55, and a 34.0% reduction in absolute risk, or absolute risk reduction (ARR)=0.34.

NNT analysis of data from the probiotic and placebo groups revealed that the number needed to treat is 3. On average, three patients would need to receive Lacto-G Forte to prevent one additional patient from developing antibiotic-associated diarrhea.

The average time to resolve diarrhea in the Lacto-G Forte group was 1.38±0.62 days and in the placebo group - 2.37±0.84 days.

During the study (active treatment and follow-up period), no adverse events were observed in the probiotic and placebo groups.

DISCUSSION

Elderly patients have decreased immune function, poor body resistance, and gradually disordered intestinal flora. External factors easily affect them, leading to dysbacteriosis and diarrhea symptoms.[14] In treating pneumonia in the elderly, patients are treated with broad-spectrum antibiotics due to the unclear pathogenic bacteria. The duration of treatment may be extended, and the dosage may be significant, which can easily cause intestinal flora imbalance and produce AAD symptoms.[15] In recent days, many probiotics have been used in the treatment of elderly patients with pneumonia to prevent the occurrence of AAD symptoms.[16]

Probiotics play a protective role in patients' intestines and stomachs, indirectly improving the symptoms caused by antibiotic use and enhancing their immune function. Probiotics can improve treatment efficacy in elderly patients with pneumonia, indicating that by taking probiotics, patients' gut microbiota is improved, and the effect of pneumonia treatment is indirectly improved.

Probiotics containing *lactobacilli* and *bifidobacteria* help maintain and restore the physiological balance of normal intestinal flora. They produce lactic and acetic acid, creating unfavorable conditions for the reproduction and survival of pathogenic microbes in the intestine. These microbes participate in digestion, vitamin synthesis, and electrolyte balance, as well as in the metabolism of proteins, phospholipids, bile and fatty acids, bilirubin, and cholesterol.

Fructooligosaccharides, which are included in the probiotics as an auxiliary substance, are natural polysaccharides and represent prebiotics - a favorable environment for the reproduction, colonization, and activity of eubiotics, i.e., intestinal bacteria. Fructooligosaccharides are distinguished by their resistance to the effects of gastric juice and, after ingestion, reach the lower part of the digestive tract unchanged.[17]

Lacto-G Forte is a generic medicine. The company (UAS Laboratories LLC, USA), which produces its intermediate product (live *lactobacilli* and *bifidobacteria*), has conducted several preclinical and clinical studies. The results of the studies confirmed the safety and clinical efficacy of the intermediate product (live *lactobacilli* and *bifidobacteria*).[18,19]

This study showed that incorporating probiotics in treating pneumonia had beneficial effects. The principal finding is that using probiotics reduces the risk of AAD, with an RRR of 0.55.

CONCLUSIONS

Lacto-G Forte supplementation in elderly patients with pneumonia reduces the risk of developing antibiotic-associated diarrhea and the time it takes to resolve, and it is safe to use.

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