Cholesterol Supplementation can Alleviate the Severity of Pulmonary Infection of Patients with Hypocholesterolemia

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Abstract
Background: Decreased concentrations of total cholesterol concentration could occur in the course of some illness, especially the infection illness. Low cholesterol concentration has been associated clinically with several adverse outcomes. We conducted a study to supplement cholesterol, and observe the change on the test indexes and the severity of disease. We then further discussed the relationships among the supplementation on cholesterol and pro- and anti-inflammatory cytokines.

Methods: A randomized and controlled clinical trial was conducted at the infectious disease department in Beijing Friendship Hospital, Capital Medical University, Beijing. Between January 2011 and December 2012, all hospitalized patients with pulmonary infection were invited. The patients were assigned into intervention group and control group randomly. After 10-day supplementation and observation, we analyzed the changes of clinical measurements.

Results: In the intervention group, there were statistically significant increases in concentration of total cholesterol (TC), albumin (ALB), pre albumin (PA) after 10-day intervention of cholesterol supplementation (P<0.05). The concentration of C reactive protein (CRP), interleukin-6 (IL-6), and the severity of disease by Simplified Acute Physiology Score II (SAPSII) assessment after intervention were significant lower than those before intervention (P<0.05). The concentration of interleukin-10 (IL-10) increased in a trend (P=0.074), but had no significant difference. In the control group, the data showed that TC, PA and CRP had changes in trend after 10-day observation (P<0.1), but the changes had no significance (P>0.05). Compared the differences on indexes between after 10-day intervention in intervention group and after 10-day observation in control group, the compared data showed that there were significant differences in seven indexes, TC, Body Mass Index (BMI), ALB, PA, CRP, IL-6 and the severity of disease (P<0.05). The increased concentrations of TC, ALB and PA in intervention group were more than those changes in control group. The BMI in intervention group was increased more than that in control group. The decreased concentrations of CRP and IL-6 in intervention group were more than those changes in control group. The improvement of severity of disease in intervention group was more obvious than that in control group. The improvement of nutrition status in intervention group was significant.

Conclusion: Infectious disease, especially pneumonia and pulmonary infection disease, can lead to hypocholesterolemia. Supplementation of cholesterol properly can improve the nutritional status, decrease the severity of disease, and improve the prognosis of disease.

Keywords: hypocholesterolemia, pulmonary infection, nutritional status, severity of disease

Cite This Article: Jia Wang, and Zhong-xin Hong, “Cholesterol Supplement can Alleviate the Severity of Pulmonary Infection of Patients with Hypocholesterolemia.” Journal of Food and Nutrition Research, vol. 4, no. 3 (2016): 131-136. doi: 10.12691/jfnr-4-3-1.

1. Introduction

Cholesterol constitutes up to 30% of the total lipid content in the cell membrane, and participates in the fluidity of this structure. Consequently, cholesterol is involved in the activity of membrane-bound enzymes and membrane functions such as phagocytosis and cell growth.

There are two sources of cholesterol in the body. One is exogenous cholesterol from the animal food intake, the other is endogenous cholesterol from the synthesis of body organ (liver and intestine) [1]. In general, the cholesterol level in the body is in a dynamic balance. When the intake of cholesterol is more, the synthesis of cholesterol in the body will decrease. When the intake of cholesterol is less, the synthesis of cholesterol in the body can increase.

Low cholesterol is common in hospitalized patients. According to the test standard in Beijing Friendship Hospital, when the blood cholesterol level of a patient is below 3.9mmol/L, he or she will be diagnosed as hypocholesterolemia. Our previous research found that, in our hospital inpatients, the incidence of hypocholesterolemia was high (37.8% of the research inpatients). Hypocholesterolemia is a sensitive evaluation marker in hospitalized patients with nutritional deficiency malnutrition. Its predictive value for nutritional status is better than the traditional indexes (e.g. low plasma
albumin level). It can be found timely intervention can improve the prognosis of patients with early malnutrition [2].

At present, many patients use limited cholesterol intake diet (cholesterol intake less than 300mg/d) and / or take statins drugs to control the plasma cholesterol level to reduce the incidence of disease of cardiovascular disease. However, this diet control may not be appropriate. The level of plasma cholesterol lower than the minimum standard is defined as hypocholesterolemia, which could have a negative effect on the prognosis of disease.

Hypocholesterolemia is correlated to the exacerbation of many diseases. Gordon et al. [3,4] observed that concentrations of total and lipoprotein cholesterol decline markedly in the early phases of many critical diseases. Researchers also found that cholesterol metabolism could lead to inflammation [5,6,7], and indeed, may regulate and be regulated by proinflammatory cytokines [8,9,10,11]. Muldoon et al. [12] found that hypocholesterolemia may cause the immune function abnormal. The main performances include, the total number of lymphocytes decreased, T lymphocyte count decreased, CD8+ cell count decreased and the activity of those reduced. Low cholesterol concentration is associated with many clinical outcomes, including death, development of nosocomial infection, increase of length of intensive care unit stay, to immune dysfunctions, and the exacerbation of the magnitude of organ dysfunction [3,13]. Dunham et al. [14] found that low serum cholesterol concentrations in non-survivors is correlated with the onset of nosocomial infection and an increasing magnitude of organ dysfunction, and an increased cholesterol concentration during convalescence. Giovannini et al. [15] found that the surgical patients with sepsis, liver dysfunction or multiple organ dysfunction usually had a low cholesterol concentration. The patients with hypocholesterolemia suffer from the respiratory disease increased significantly. One major reason was that the patients with hypocholesterolemia had abnormal immune function and the synthesis of alveolar surface active material was reduced [16]. Patients with community-acquired pneumonia also manifest hypocholesterolemia. Rodriguez Reguero et al. [17] observed lipid profile over a 6-month period in 60 patients with community-acquired pneumonia. Concentrations of total and High Density Lipoprotein-Cholesterol (HDL-C) and a apolipoproteins A1 and B were all decreased during the acute infection. The incidence of hypocholesterolemia in patients with respiratory disease is obviously higher than other disease patients.

The mechanism of hypocholesterolemia during infection could be multifactorial, with both decreased synthesis and increased catabolism playing a role. It may be associated with the following aspects: ① when the body suffers from disease especially serious infectious disease, the decomposition hypermetabolism and energy consumption increases. The body produces the energy mainly from the fatty acid oxidation, and the decomposition of fat increases significantly [18,19]. Infection and inflammation induce oxidation of Low Density Lipoprotein-Cholesterol(LDL-C) [20,21]. ② Lack of a precursor of the synthesis of cholesterol. When the body suffers from severe stress, the utilization of carbohydrate has obstacle, the raw materials to synthesis cholesterol, such as acetyl coa and ATP reduce significantly. These cause the cholesterol level decreases. ③ The effect of hormone. The metabolism of lipid is regulated by hormone. When the body suffer from the serious stress, the secretion of epinephrine, norepinephrine, and glucocorticoid increase. This can accelerate the fat decomposition. And the body can increase the ability to clear the cholesterol in the blood. ④ The role of cytokines. Bonville et al. [18] observed that the decreased of cholesterol level was related to the elevation of some cytokines, such as interleukin-6 (IL-6) and IL-10. ⑤ The role of free radicals. When the body suffers from the serious stress, the body produce a large number of free radicals, such as oxygen free radicals. It can play a role on the biological membrane directly or indirectly. The function of biological membrane will be impaired, and the cholesterol on the biological membrane will be depletion. ⑥ Decreased lipoprotein synthesis occurs in vitro when hepatocytes are exposed to Tumor Necrosis Factor (TNF) and IL-6. [22] ⑦ When the synthesis of cholesterol is disordered caused by the disease, the exogenous cholesterol from the animal food intake is very important to maintain the plasma cholesterol level. In the period of infectious disease, especially in the acute period, the reduction of the food intake or the food rich in cholesterol intake can influence the cholesterol intake, and lead to the hypocholesterolemia.

At present, the patients with low cholesterol level had no special supplementation diet therapy or enteral nutrition therapy. There is no research on improving the nutritional status and the severity of disease in pulmonary infection patients with low cholesterol concentration through supplementing cholesterol.

Although the correlation between hypocholesterolemia and respiratory disease is well known, whether special supplement diet therapy or enteral nutrition therapy for hypocholesterolemia could alleviate the disease progress have not been well studied.

In this study, we explored the effects of cholesterol supplementation on hospitalized patients with pulmonary infection. We conducted a randomized controlled clinical trial and compared the changes of nutrition status and disease severity of the intervention group with the control group. We further explored the relationships among the supplementation on cholesterol and pro- and anti-inflammatory cytokines.

2. Materials and Methods

2.1. Participants

We conducted a randomized controlled clinical trial in the Department of infectious disease in Beijing Friendship Hospital, Capital Medical University. Between January 2011 and December 2012, all hospitalized patients with pulmonary infection were invited to enter the study. The inclusion criteria were as follows: (1) age of ≥18 y; (2) the serum total cholesterol level<3.9mmol/L; (3) the nutritional status assessment is poor by application of Subjective Global Assessment (SGA) evaluation method [23]; (4) the patients eating by mouth or with enteral nutrition; (5) no serious liver or kidney illness; (6) disease status and therapy: genuine pneumonia(two sides of lung),...
have fever with the temperature over than 38°C, have symptoms such as cough, expectoration and pectoralgia. Using piperacillin/Tazobactam, ambroxol, and oxygen inhalation. (7) the patients who agree to participate this research and sign the informed consent. The exclusion criteria were as follows: (1) had cognitive impairment; (2) the patients with pregnancy or lactation period; (3) cancer patients; (4) patients with pulmonary infection after surgery; (5) patients with important organ complications; (6) either phenytoin (raises cholesterol concentration) or statin drugs (lowers cholesterol concentration) were administered recently or concurrently; (7) the patients with respiratory failure.

According to the pre experiment, the confidence level is 99%, which is a significant level of α=0.01, allowing error of the index, the standard deviation is 0.87. n=(Z1-α/2·σ/δ)²=(2.58×0.86/0.5)²=19.69. So, the sample of experiment group set to 20 cases.

With the inclusion criteria and exclusion criteria, 47 patients were enrolled in our study. They were randomly divided into intervention group (with supplementation of cholesterol) and control group (without supplementation of cholesterol) with the method of random number.

The study was approved by the ethical committee of Beijing Friendship Hospital, Capital Medical University. All participants had written the informed consent.

2.2. Method

We applied the simplified acute physiology score II (SAPS II) to assess the severity of the disease. SAPS II is consist of two parts: SAPS II score and PHM computation. SAPS II is consist of 17 variables, including 12 physiological variables, age, the type of admission and three chronic diseases, AIDS, metastatic carcinoma and blood malignant tumor. The higher score indicates that the more serious illness and the worse the prognosis.

SAPS II computed as follows:

\[ \text{SAPS II} = \frac{\text{weight} \times \text{age} \times \text{temperature coefficient} \times \text{stress coefficient}}{1000} + \text{temperature coefficient} \times \text{stress coefficient} \]

We used the assessment of SGA to assess the nutritional status. SGA assesses the nutritional status according to the patient’s medical history and symptoms. It includes eight aspects: the change of weight in the past two weeks, the dietary intake, the ability of activity, the stress reaction, the reduction of subcutaneous fat, the reduction of muscle, and the ankle edema. In our study, the assessment standard of SGA was decided by the different quality dietitians. We categories patients into three nutrition levels: (1) good nutrition level - patients who experienced moderate weight loss and muscle wasting, but recently eat enough and have weight gained; (2) medium nutrition level - patients who experienced moderate weight loss, lack of feeding continue, weight declined, dysfunction continue, and had moderate stress diseases; (3) poor nutrition level - patients who experienced severe weight loss, lack of nutrient intake continue, dysfunction continue, muscle wasting continue, and all these changes did not result from the disease state of stress [23].

We took phlebotomize 10ml of each patient in the next day morning after he/she had been admitted. We used automatic biochemical analyzer Olympus 5400 to test each patient’s blood, and recorded the plasma total cholesterol level(TC), the plasma low density lipoprotein cholesterol (LDL-C), the plasma high density lipoprotein cholesterol (HDL-C), triglyceride (TG), serum albumin (ALB), serum prealbumin (PA), hemoglobin (Hb), lymphocyte count (Ly) and high sensitive C reactive protein level (CRP). According to the reference range in our hospital, we diagnosis patient whose TC<3.9mmol/L to have hypocholesterolemia. We measured body weight while the participants were wearing light clothing and no shoes. We used a stadiometer to measure height without shoes. We calculated body mass index (BMI) as weight divided by the square of height. We used skinfold instrument to measure triceps skinfold thickness(TSF). Patients were taken other phlebotomize 6ml to determine cytokine, interleukin-1(IL-1), IL-2, IL-6, IL-10 and tumor necrosis factor(TNF) using ELISA. Then we compared the difference of the age, gender, TC and the severity of the disease between intervention group and control group.

With the same standard (including exercise coefficient and stress coefficient), we designed the daily total energy intake and the whole daily food for each patient. The whole daily food include staple food, milk, egg, meat, fish, bean, vegetable, fruit and duts. Two group provide the same amount of egg and meat. Then, we compared the difference of the total energy and macronutrients intake between intervention group and control group. In intervention group, we supplemented extra 600mg cholesterol per day (provided by the egg yolk). For the control group, we did not supplement extra cholesterol in addition to the standard daily food and instead of placebo made of corn flour (supples VitA). The experiment was performed for 10 days.

BEE(male)=66.47×(13.75×W)+(5.00×H)-(6.76×A)

\[ \text{BEE(male)} = 66.47 \times (13.75 \times W) + (5.00 \times H) - (6.76 \times A) \]

BEE(female)=655.10×(9.56×W)+(1.85×H)-(4.68×A)

\[ \text{BEE(female)} = 655.10 \times (9.56 \times W) + (1.85 \times H) - (4.68 \times A) \]

\( W \) represent weight, \( H \) represent height, \( A \) represent age.

Daily energy intake=BEE×exercise coefficient × temperature coefficient × stress coefficient

Exercise coefficient standard: lie in bed 1.2, get out of the bed and have a small amount of activity 1.25, normal activity 1.3

Temperature coefficient standard: 38°C 1.1, 39°C 1.2, 40°C 1.3, 41°C 1.4.

Stress coefficient standard (to correct the various disease states of BMR). In our experiment, the research objects were all pneumonia patients, no operation, cancer, peritonitis, fracture, multiple trauma, burn patients. The stress coefficient set to 1.

Protein intake standard: 1.0g/kg ideal body weight, and the high quality protein accounted for 1/2.

Carbohydrate intake standard: the total energy of 50-60%, with the complex carbohydrate.

Fat intake standard: the total energy below 30%.

In control group, we gave the patients one egg per day. In intervention group, we gave the patients one egg per day and extra 600mg cholesterol from egg yolk.

After 10 days, we assessed the severity of the disease and the nutritional status. Then took phlebotomize to test TC, LDL-C, HDL-C, TG, ALB, PA, Hb, Ly, CRP, IL-1, IL-2, IL-6, IL-10 and TNF. And measured the body weight, height and TSF again.

2.3. Statistical Analysis

The differences of the nutrition measurements before intervention between intervention group and control group were analyzed with Student’s t test. The changes on the
before and after intervention in intervention group and the before and after observation in control group were analyzed with pair Student’s test respectively, respectively. We used Wilcoxon two samples comparison method to analyze the difference between before and after intervention in intervention group and the difference between before and after observation in control group. We used chi-square test to compare the difference of SG A between after intervention in experiment group and after observation in control group. Data are presented as means ± SDs. The 2-tailed significance threshold was set as P<0.05. All statistics were calculated with the use of the STATISTICAL PACKAGE FOR SOCIAL SCIECES (SPSS for Windows, version 17.0; SPSS, Chicago, IL).

### Table 1. The Comparison of clinical data Intervention Group (IG) and Control Group (CG)

<table>
<thead>
<tr>
<th>group</th>
<th>No</th>
<th>TC (mmol/L) before</th>
<th>TC (mmol/L) after</th>
<th>BMI (kg/m²) before</th>
<th>BMI (kg/m²) after</th>
<th>TSF (mm) before</th>
<th>TSF (mm) after</th>
<th>ALB (g/L) before</th>
<th>ALB (g/L) after</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG</td>
<td>27</td>
<td>3.24±0.64</td>
<td>3.27±0.61</td>
<td>22.7±3.4</td>
<td>22.0±3.2</td>
<td>9.9±2.6</td>
<td>9.9±2.6</td>
<td>33±4</td>
<td>34±4</td>
</tr>
<tr>
<td>IG</td>
<td>20</td>
<td>3.39±0.37</td>
<td>4.17±0.98</td>
<td>21.7±3.2</td>
<td>21.7±3.2</td>
<td>9.2±3.2</td>
<td>9.7±2.2</td>
<td>32±4</td>
<td>36±7</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>0.941</td>
<td>2.520</td>
<td>-0.931</td>
<td>-0.910</td>
<td>-0.812</td>
<td>0.680</td>
<td>-0.91</td>
<td>2.020</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.354</td>
<td>0.015</td>
<td>0.356</td>
<td>0.364</td>
<td>0.426</td>
<td>0.499</td>
<td>0.364</td>
<td>0.047</td>
</tr>
</tbody>
</table>

### Table 2. The Comparison of Total Energy and Nutrients Intake Between Intervention Group and Control Group

<table>
<thead>
<tr>
<th></th>
<th>Total energy intake</th>
<th>Carbohydrate intake</th>
<th>Protein intake</th>
<th>Fat intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention Group</td>
<td>1730.0±212.9</td>
<td>253.0±30.6</td>
<td>60.8±5.8</td>
<td>53.1±9.6</td>
</tr>
<tr>
<td>Control Group</td>
<td>1770.4±281.2</td>
<td>260.9±45.1</td>
<td>62.5±9.8</td>
<td>53.2±8.7</td>
</tr>
<tr>
<td>t</td>
<td>-0.537</td>
<td>-0.681</td>
<td>-0.678</td>
<td>-0.048</td>
</tr>
<tr>
<td>P-value</td>
<td>0.594</td>
<td>0.500</td>
<td>0.501</td>
<td>0.962</td>
</tr>
</tbody>
</table>

3. Result

Before intervention and observation, the comparability of age, gender, severity of disease, TC, LDL-C, HDL-C, TG, BMI, TSF, ALB, Pa, Ly, Hb, CRP, IL-1, IL-2, IL-6, IL-10 and TNF between intervention group and control group were analyzed. The result showed that there was no significant difference between two groups on these indexes (P>0.05) (Table 1). After intervention and observation, the TC, ALB, Pa, hs CRP, IL-6 and the severity of disease had significant difference between two groups (P<0.05) (Table 1).

We used χ² test to compare the change on nutritional status between after intervention in intervention group and after observation in control group. The data showed that compared with the control group, the improvement of nutrition status in intervention group was significant (Table 3).
Table 3. The Change of Nutrition Assessment Score Between After Intervention in Intervention Group and After Observation in Control Group (n)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>A+B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention group</td>
<td>20</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Control group</td>
<td>27</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td></td>
<td>4.984</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.046</td>
<td></td>
</tr>
</tbody>
</table>

Note: A nutrition well, B nutrition moderate, C nutrition poor.

4. Discussion

In our study, the plasma cholesterol concentration increased significantly after 10-day cholesterol supplementation. In the control group, after 10-day observation, the plasma cholesterol concentration increased in a trend. But when we used Wilcoxon two samples comparison method to analyze the D-value between before and after data, compared with the control group, the elevation level of plasma cholesterol had a significant difference. This result showed that, as the improvement of disease, the cholesterol consumption can reduce, and the plasma cholesterol concentration will have a slightly rising. This result is consistent with the Dunham et al. [14] research, which have found that increased cholesterol concentration could occur during convalescence. Supplementation of proper cholesterol can greatly improve the state of low cholesterol levels.

The change of CRP in our study has the same trend with the change of cholesterol level. In control group, after 10-day observation, the level of CRP had decreased in a trend. In intervention group, CRP level had a significant decrease. After analysis of group t test, compared with the control group, CRP level in intervention group decreased obviously. This phenomenon showed that, with the improvement of disease, CRP level can decrease, but in supplemental group, the decrease level of CRP was obvious. It may be herald that the complement of cholesterol in disease, especially in infection disease, can improve the prognosis of disease.

In our research, we also analyzed the severity of disease. The result showed that, in intervention group, supplementation could significantly decrease the severity of disease. While in control group, the decrease had a trend, and had no significant difference. Group t test result showed that, compared with the change in control group, the supplementation of cholesterol can obviously decrease the severity of disease. So proper supplementation of cholesterol can improve the severity of disease.

In our research, we analyzed the nutritional status change. In intervention group, BMI after intervention had no significant difference, while plasma ALB and PA had both elevate obviously. In control group, BMI and plasma ALB after observation decreased in a trend, and plasma PA increased in a trend. Group t test results showed that, compared with the data in control group, the change in intervention group on the BMI, plasma ALB and PA had significant difference. We also used SGA to assess the nutritional status. In intervention group, the patients with assessment of A and B after intervention were more than the number in the control group. This result showed that the restore nutritional status in intervention group was better than that in control group. Combining with the change of BMI, plasma ALB and PA, supplementation of cholesterol can obviously improve patients’ nutritional status.

The analysis above found that, supplementation of proper cholesterol can decrease the severity of disease, and improve patients’ nutritional status. The mechanism may be associated with the following aspects. ①The surface activity material, maintain lung elasticity, is mainly composed of cholesterol. Therefore, when the cholesterol level is lower than normal, the elasticity of lung will decrease [15]. After supplementation of cholesterol, the flexibility of the lung can improve effectively. The ability of removing a foreign body strengthens. This can decrease the severity of disease. ②The role of cytokines. Bonville et al. [18] observed that the decreased of cholesterol level was related to the elevation of some cytokines, such as IL-6 and IL-10. In our research, the result showed that, after supplementation of cholesterol, the plasma cholesterol concentration increased properly. The proinflammatory cytokines IL-6 in intervention group had decreased significant, while in control group, IL-6 had increased in a trend. At the same time, the anti-inflammatory cytokine IL-10 in intervention group increased in a trend, while in control group, IL-10 had no change. This proved that when the plasma cholesterol concentration increased after supplementation, the decrease of proinflammatory cytokine and the increase of anti-inflammatory cytokine could improve the severity of disease. ③In intervention group, the nutritional status had a significant improvement. This is beneficial for the disease treatment, such as pneumonia and pulmonary infection.

Supplementation of cholesterol properly can increase the plasma cholesterol concentration, improve the nutritional status, decrease the severity of disease, and improve the prognosis of disease. In the treatment of infection disease, the clinic may improve the low plasma cholesterol as a new therapeutic target. But in the early research we found that, in clinical practice, the doctors have not fully realized the impact of low cholesterol level, and have not considered supplementation cholesterol treatment for hypcholesterolemia patients. Research found that hypcholesterolemia usually happened in the patients who use the enteral nutrition and parenteral nutrition support (52%) [24]. At present, the enteral and parenteral nutrition preparations for the types of fat are usually long chain triglycerides, medium chain triglycerides, glycerin monoester and diglyceride. And no nutrition preparations contain amount of cholesterol. So the patients in long-term application of enteral or parenteral nutrition support with the critically ill is easily insufficient of exogenous cholesterol intake, which could lead to hypcholesterolemia. In domestic and international, there are no research on supplementation of cholesterol in patients with low cholesterol concentration to improve the nutritional status and severity of disease. There is no regular supplementation of cholesterol standard. And in any nutrition preparation, enteral nutrition or parenteral nutrition, there is no supplementation cholesterol preparation. In our intervention study, we just do the research on the supplementation of cholesterol and disease severity. In future, we will study different doses of cholesterol for different levels of cholesterol concentration.
to provide standard clinical guideline and extract cholesterol from food to made goods preparation.

Hypocholesterolemia is correlated to the exacerbation of pneumonia and pulmonary infection disease. Supplementation of cholesterol properly can improve the nutritional status, alleviate the severity of disease, and it is beneficial for disease treatment.

Acknowledgement

The research is supported by the college fund of Beijing Friendship Hospital.

References


