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# Effects of *Lactobacillus casei* on Hematology and Blood Chemistry in Normal and Burned Mice

Yoshiya HORIKAWA, Hajime SAITO and Takashi WATANABE
*Department of Microbiology and Immunology, Shimane Medical University, Izumo 693, Japan*
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## ABSTRACT

Effects of the bacterial immunostimulant, *Lactobacillus casei* YIT 0003 (viable), on hematology and blood chemistry in normal and full thickness burned mice were studied. The white blood cell counts in normal and burned mice pretreated with *L. casei* cells at an early period after the intraperitoneal or subcutaneous administration of the cells were higher than in untreated animals. Significant increases in the population of neutrophils occurred in both groups of mice, at this period. On the other hand, *L. casei* cells did not affect red blood cell counts, platelet counts, plasma components, enzyme activities and electrolytes.

*Lactobacillus casei* cells will activate macrophages[6,15], enhance antibody production[10] and natural killer cell cytotoxicity[7], in addition to possessing antitumor activity[5].

In previous studies[3,11-13,15,16], we found that *L. casei* cells enhanced the resistance to opportunistic infections in normal and immunodeficient mice subjected to thermal injury, implantation of sarcoma 180 cells or administration of dexamethasone, in high doses. For the clinical use of *L. casei* cells, as immunostimulants, it is indispensable that there is no toxic effect.

This paper deals with the effects of *L. casei* cells on hematology and blood chemistry, in normal and burned mice.

*L. casei* YIT 0003 cells grown in Rogosa's broth[2] at 37°C for 24 hr were washed twice with saline, suspended in saline and serially diluted 10-fold with saline, the number of colony-forming units was determined on Rogosa's agar plate. Each of 5-week-old female ddY mice (n=10), purchased from the Shizuoka Agricultural Cooperative for Experimental Animals, Shizuoka, Japan, was injected intraperitoneally (ip) with 0.1 ml of a viable *L. casei* cell suspension ($3.2 \times 10^8$/ml) once daily for 3 days. At various intervals after the last injection, mice were anesthetized with ether, and blood samples were taken by cardiac puncture using a heparinized syringe. Hematocrit (Hct), hemoglobin (Hgb), red blood cells (RBC), white blood cells (WBC) and platelet (PLT) counts were mode using a coulter counter (Model S-plus, Coulter Electronics Co., U.S.A.). Leucocyte differential was determined microscopically with blood smears stained with Wright's solution. Total protein was determined using Biuret's method, albumin using the BCG method, total cholesterol the COD-POD method, urea nitrogen the urease-ultraviolet method, glutamic oxaloacetic transaminase (GOT) the MDH-ultraviolet method and alkaline phosphatase (ALP) the Rate's method, that is the Ultralab system (Model 2086 Mark II, LKB Co., Sweden). Electrolytes such as Na, K and Cl were measured using an Electrolyte Analyzer (Type PVA-4, Photovolt Co., U.S.A.).

As shown in Table 1, no significant differences in the number of WBC, RBC and PLT counts and the amounts of Hgb and Hct were noted between viable *L. casei*-administered and untreated normal mice, throughout the entire

**Table 1.** Comparison of hematology in normal mice pretreated intraperitoneally with or without viable *L. casei* cells

| | Days after the administration of *L. casei* | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | | 3 | | 5 | | 7 | | 14 | |
| | | C* | E** | C | E | C | E | C | E | C | E |
| WBC ($\times 10^3$/mm$^3$) | 6.5±0.8 | 7.1±1.2 | 5.1±1.0 | 6.1±0.6 | 5.5±0.6 | 6.0±1.2 | 6.3±0.7 | 5.1±0.2 | 7.5±0.6 | 7.6±0.6 | 6.4±0.4 |
| RBC ($\times 10^6$/mm$^3$) | 7.9±0.3 | 8.2±0.1 | 8.1±0.1 | 8.1±0.1 | 7.8±0.4 | 8.1±0.2 | 8.2±0.1 | 8.3±0.1 | 8.0±0.1 | 9.0±0.1 | 8.6±0.2 |
| Hgb g/dl | 14.3±0.4 | 13.5±0.4 | 14.1±0.2 | 14.6±0.2 | 14.8±0.3 | 14.5±0.3 | 14.6±0.1 | 14.7±0.1 | 14.4±0.2 | 16.1±0.3 | 15.3±0.3 |
| Hct % | 40.4±1.2 | 42.4±0.7 | 42.6±0.7 | 39.3±0.5 | 39.2±0.6 | 38.7±0.8 | 38.9±0.4 | 39.5±0.4 | 38.5±0.5 | 43.7±0.7 | 41.5±0.7 |
| PLT ($\times 10^5$/mm$^3$) | 9.8±0.1 | 7.6±0.5 | 7.3±0.6 | 9.0±0.4 | 9.6±0.3 | 8.7±0.3 | 8.3±1.0 | 8.8±0.4 | 9.1±0.2 | 8.4±1.0 | 9.4±0.4 |
| *Hemogram (%)* | | | | | | | | | | | |
| Neutrophil | 11.0±1.3 | 9.6±1.1 | 13.4±0.8 | 11.9±1.6 | 16.3±0.5 | 11.5±2.1 | 12.0±0.7 | 12.4±1.5 | 9.6±0.5 | 9.3±0.9 | 7.8±0.4 |
| Eosinophil | 2.3±0.5 | 3.4±0.7 | 1.0±0.4 | 1.6±0.3 | 1.6±0.4 | 1.8±0.4 | 2.8±0.5 | 3.3±0.7 | 2.4±0.4 | 3.5±0.3 | 1.5±0.4 |
| Basophil | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lymphocyte | 84.8±1.4 | 84.8±1.4 | 83.7±2.6 | 84.7±1.4 | 81.0±1.5 | 85.3±2.2 | 84.0±2.5 | 82.8±1.9 | 86.4±1.8 | 86.4±0.8 | 89.5±1.3 |
| Monocyte | 1.9±0.5 | 2.2±0.4 | 1.9±0.3 | 1.7±0.5 | 1.3±0.4 | 2.5±0.5 | 1.3±0.3 | 1.5±0.4 | 1.6±0.4 | 0.8±0.2 | 1.3±0.4 |

* Control group, ** Experimental group, values = mean ± S.E.(n=10).

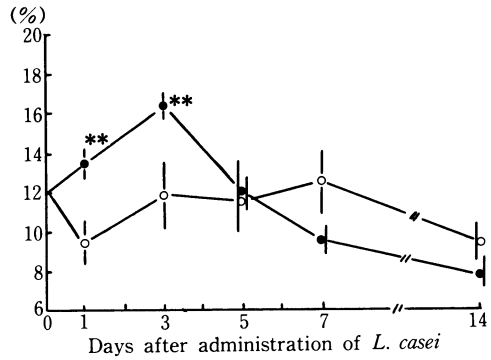


**Fig. 1.** Changes in the population of neutrophils in normal mice pretreated ip with viable *L. casei* cells.

Normal mice were injected ip with (●) or without (○) viable *L. casei* cells ($3.2 \times 10^7$). At indicated intervals, mice were anesthetized with ether and blood samples obtained. The population of neutrophils was determined as described in the text. *P* values were calculated by Student's *t*-test. Bar: mean ± S.E. (n=10), ** $p<0.01$.

experiment. In leucocyte-cell populations, neutrophils in *L. casei*-administered mice increased from 11.0% (0 time) to 16.3% 3 days after ($p<0.01$) and reverted to the level in control mice 5 days after the last administration of *L. casei* cells (Fig. 1). There were no differences in other leucocyte populations between the two groups. Table 2 shows the values of various blood chemical components in control and *L. casei*-administered mice, throughout the entire experiment. The values of components tested were not significantly altered during 14 days after the administration of viable *L. casei* cells. Hematological and blood chemical data obtained from normal ddY mice in the present studies were in agreement with findings in ICR-JCL mice[8].

We also examined the effects of viable *L. casei* cells on hematology and blood chemistry, in burned mice. Burned mice were prepared as described[3]. Briefly, the clipped dorsum of 5-week-old female ddY mice (n=7/group) anesthetized with pentobarbital (about 60 mg/kg) was burned with an iron trowel (2 × 3 cm) heated in a Bunsen burner flame for 3 sec. Approximately 10% of the total surface had a full thickness burn. One-tenth ml of viable *L. casei* ($10^{10}$/ml) was injected under the eschar of burn wounds in these mice 3 hr later. After the injection, mice were anesthetized with ether, and blood samples were obtained by cardiac puncture, at various intervals. Hematological and blood chemical tests were then done. The results obtained are summarized in Table 3. No significant differences were observed in values of hematological and blood chemical examinations between normal and burned mice, except for WBC, neutrophils. GOT and GPT. The number of WBC in the burned mice significantly decreased one day after ($p<0.05$) and reverted to the level of that in normal mice 5 days after the burn (Fig. 2). As shown in Fig. 3-A, the population of neutrophils in burned mice increased one day after and this high level was retained for 14 days after burn ($p<0.01$). In contrast, the population of lymphocytes in burned mice was significantly low as compared with lev-

**Table 2.** Comparison of blood chemistry in normal mice pretreated intraperitoneally with or without viable *L. casei* cells

| | | Day after administration of *L. casei* | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 1 | | 3 | | 5 | | 7 | | 14 | |
| | | | C* | E** | C | E | C | E | C | E | C | E |
| Total protein | g/dl | 5.4 | 5.0 | 5.2 | 5.2 | 5.2 | 5.1 | 5.6 | 4.9 | 4.9 | 4.7 | 4.7 |
| Albumin | g/dl | 2.8 | 2.6 | 2.5 | 2.7 | 2.6 | 2.7 | 3.0 | 3.0 | 2.9 | 2.8 | 2.8 |
| Total cholesterol | mg/dl | 107 | 98 | 106 | 86 | 96 | 99 | 102 | 101 | 104 | 119 | 105 |
| Urea nitrogen | ml/dl | 21 | 16 | 17 | 18 | 25 | 20 | 20 | 18 | 20 | 22 | 23 |
| GOT | IU | 41 | 53 | 88 | 78 | 53 | 51 | 46 | 67 | 65 | 67 | 50 |
| GPT | IU | 19 | 23 | 34 | 21 | 16 | 19 | 21 | 15 | 16 | 15 | 16 |
| ALP | IU | 456 | 454 | 313 | 342 | 418 | 320 | 352 | 326 | 381 | 350 | 334 |
| *Electrolytes* | | | | | | | | | | | | |
| Na | mEq/liter | 159 | 163 | 160 | 164 | 160 | 157 | 160 | 161 | 167 | 162 | 168 |
| K | mEq/liter | 5.9 | 5.0 | 5.0 | 3.6 | 4.1 | 5.0 | 5.2 | 3.9 | 3.9 | 4.1 | 4.7 |
| Cl | mEq/liter | 122 | 128 | 124 | 86 | 122 | 99 | 127 | 101 | 127 | 119 | 132 |

* Control group, ** Experimental group, values = mean in pooled plasma.

**Table 3.** Comparison of hematology and blood chemistry in normal and burned mice

| | Days after burn | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 3 hr after | | 1 | | 3 | | 5 | | 7 | | 14 | |
| | N* | B** | N | B | N | B | N | B | N | B | N | B |
| WBC ($\times 10^3$/mm$^3$) | 5.0±0.6 | 5.1±0.6 | 7.0±0.5 | 4.3±0.7 | 5.4±0.6 | 4.5±0.4 | 5.7±0.9 | 7.1±1.1 | 7.2±0.6 | 6.2±0.5 | 6.1±0.5 | 6.0±0.6 |
| RBC ($\times 10^6$/mm$^3$) | 7.8±0.2 | 9.1±0.3 | 7.8±0.1 | 7.4±0.1 | 7.8±0.1 | 7.8±0.2 | 8.2±0.3 | 7.2±0.8 | 8.4±0.1 | 7.5±0.3 | 8.9±0.1 | 7.7±0.2 |
| Hgb (g/dl) | 13.7±0.3 | 16.3±0.7 | 14.0±0.2 | 13.6±0.2 | 13.8±0.1 | 13.7±0.3 | 14.4±0.6 | 12.6±1.2 | 14.6±0.2 | 12.7±0.5 | 14.7±0.2 | 12.5±0.2 |
| Hct (%) | 39.6±1.0 | 46.8±0.9 | 37.9±0.8 | 36.9±0.6 | 40.6±0.3 | 39.3±0.9 | 41.4±1.8 | 36.3±3.5 | 42.8±0.7 | 32.9±5.0 | 42.4±0.6 | 37.4±0.6 |
| PLT ($\times 10^5$/mm$^3$) | 9.7±0.2 | 8.5±0.7 | 8.9±1.1 | 8.2±0.8 | 9.3±0.2 | 8.0±1.0 | 9.6±0.3 | 10.0±0 | 9.7±0.2 | 10.0±0 | 10.0±0 | 9.8±0.2 |
| *Hemogram (%)* | | | | | | | | | | | | |
| Neutrophili | 10.4±1.7 | 11.7±0.2 | 8.5±0.8 | 14.4±4.1 | 12.5±2.5 | 13.2±2.0 | 10.5±1.1 | 15.6±1.8 | 6.7±1.0 | 16.0±1.8 | 8.1±1.3 | 13.9±1.8 |
| Eosinophili | 2.9±0.5 | 2.1±0.4 | 1.4±0.4 | 1.6±0.6 | 1.1±0.3 | 2.0±0.7 | 1.2±0.2 | 1.6±0.4 | 2.1±0.5 | 1.9±0.4 | 3.1±0.3 | 2.7±0.4 |
| Basophili | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lymphocyte | 86.0±1.9 | 85.1±2.4 | 89.9±1.2 | 83.1±4.4 | 85.4±2.9 | 85.1±2.4 | 87.9±1.1 | 81.7±2.5 | 90.8±1.8 | 81.0±2.1 | 88.2±1.5 | 82.3±1.7 |
| Monocyte | 0.7±0.3 | 1.1±0.4 | 0.2±0.1 | 0.9±0.3 | 1.0±0.3 | 0.7±0.3 | 0.4±0.2 | 1.1±0.4 | 0.4±0.2 | 1.1±0.4 | 0.6±0.3 | 1.1±0.4 |
| Total protein (g/dl) | 4.8 | 4.5 | 4.7 | 4.5 | 4.9 | 4.9 | 4.7 | 4.6 | 5.0 | 4.9 | 5.1 | 4.9 |
| Albumin (g/dl) | 3.3 | 2.8 | 3.4 | 2.7 | 3.5 | 3.1 | 3.1 | 2.8 | 3.3 | 2.7 | 3.5 | 2.5 |
| Total cholesterol (mg/dl) | 102 | 96 | 119 | 96 | 110 | 110 | 116 | 111 | 111 | 100 | 106 | 105 |
| Urea N(mg/dl) | 42 | 11 | 19 | 15 | 40 | 32 | 30 | 27 | 21 | 18 | 30 | 25 |
| GOT (IU) | 83 | 269 | 78 | 235 | 80 | 132 | 102 | 151 | 106 | 120 | 83 | 60 |
| GPT (IU) | 23 | 202 | 17 | 37 | 21 | 27 | 41 | 25 | 18 | 12 | 28 | 20 |
| *Electrolytes* | | | | | | | | | | | | |
| Na (mEq/liter) | 152 | 138 | 153 | 157 | 155 | 157 | 150 | 155 | 153 | 155 | 156 | 157 |
| K (mEq/liter) | 4.7 | 4.7 | 4.6 | 5.3 | 4.7 | 5.2 | 4.6 | 5.6 | 4.8 | 4.4 | 6.4 | 5.3 |
| Cl (mEq/liter) | 117 | 106 | 117 | 120 | 118 | 121 | 114 | 118 | 120 | 120 | 121 | 120 |

* Normal mice, ** Burned mice (n=7).

**Table 4.** Comparison of hematology and blood chemistry in burned mice pretreated subcutaneously with or without viable

| | 3 hr | | Days after administration of *L. casei* | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | | 3 | | 5 | | 7 | | 14 | |
| | Normal | Burned | C* | E** | C | E | C | E | C | E | C | E |
| WBC ($\times 10^3$/mm$^3$) | 5.0±0.6 | 5.1±0.6 | 4.3±0.7 | 3.7±0.8 | 4.5±0.4 | 5.6±0.3 | 7.1±1.1 | 7.3±1.3 | 6.2±0.5 | 7.6±0.6 | 6.0±0.6 | 7.2±0.9 |
| RBC ($\times 10^6$/mm$^3$) | 7.8±0.2 | 9.1±0.3 | 7.4±0.1 | 7.5±0.5 | 7.8±0.2 | 7.7±0.1 | 7.2±0.8 | 7.3±0.3 | 7.5±0.3 | 7.6±0.5 | 7.7±0.2 | 8.2±0.2 |
| Hgb (g/dl) | 13.7±0.3 | 16.3±0.7 | 13.6±0.2 | 13.6±0.6 | 13.7±0.3 | 13.6±0.2 | 12.6±1.2 | 12.9±0.3 | 12.7±0.5 | 13.3±0.5 | 12.5±0.2 | 13.0±0.2 |
| Hct (%) | 39.6±1.0 | 46.8±0.9 | 36.9±0.6 | 37.8±2.9 | 39.3±0.9 | 39.4±0.7 | 36.3±3.5 | 37.4±0.9 | 32.9±0.5 | 39.1±1.7 | 37.4±0.6 | 40.2±1.7 |
| PLT ($\times 10^5$/mm$^3$) | 9.7±0.2 | 8.5±0.7 | 8.2±0.8 | 8.6±0.1 | 8.0±1.0 | 8.9±0.5 | 10.0±0 | 10.0±0 | 10.0±0 | 8.9±0.7 | 9.8±0.2 | 10.0±0 |
| *Hemogram (%)* | | | | | | | | | | | | |
| Neutrophil | 10.4±1.7 | 11.7±2.2 | 14.4±4.1 | 12.4±2.4 | 13.2±2.0 | 11.8±1.1 | 15.6±1.8 | 24.8±2.0 | 16.0±1.8 | 19.1±3.5 | 13.9±1.8 | 18.3±3.0 |
| Eosinophil | 2.9±0.5 | 2.1±0.4 | 1.6±0.6 | 1.4±0.3 | 2.0±0.7 | 1.8±0.6 | 1.6±0.3 | 1.9±0.4 | 3.3±0.5 | 2.7±0.4 | 2.1±0.6 | |
| Basophil | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lymphocyte | 86.0±1.9 | 85.1±2.4 | 83.1±4.4 | 84.3±6.7 | 85.1±2.4 | 85.2±1.4 | 81.7±2.5 | 73.1±2.4 | 81.0±2.1 | 76.0±3.3 | 82.3±1.7 | 79.0±3.0 |
| Monocyte | 0.7±0.3 | 1.1±0.4 | 0.9±0.3 | 1.9±0.6 | 0.7±0.3 | 1.2±0.5 | 1.1±0.4 | 0.5±0.2 | 1.1±0.4 | 1.6±0.5 | 1.1±0.4 | 0.6±0.3 |
| Total protein (g/dl) | 4.8 | 4.5 | 4.5 | 4.6 | 4.9 | 5.0 | 4.6 | 4.5 | 4.9 | 4.8 | 4.9 | 4.8 |
| Albumin (g/dl) | 3.3 | 2.8 | 2.7 | 2.5 | 3.1 | 2.7 | 2.8 | 2.8 | 2.7 | 2.8 | 2.5 | 2.2 |
| Total cholesterol (mg/dl) | 102 | 96 | 96 | 106 | 110 | 106 | 111 | 106 | 100 | 87 | 105 | 100 |
| Urea N (mg/dl) | 42 | 11 | 15 | 13 | 32 | 21 | 27 | 27 | 18 | 17 | 25 | 15 |
| GOT (IU) | 83 | 269 | 235 | 196 | 132 | 126 | 151 | 207 | 120 | 187 | 60 | 85 |
| GPT (IU) | 23 | 202 | 37 | 31 | 27 | 26 | 25 | 35 | 12 | 17 | 20 | 22 |
| *Electrolytes* | | | | | | | | | | | | |
| Na (mEq/liter) | 152 | 138 | 157 | 155 | 157 | 155 | 155 | 152 | 155 | 158 | 157 | 156 |
| K (mEg/liter) | 4.7 | 4.7 | 5.3 | 4.7 | 5.2 | 5.9 | 5.6 | 5.8 | 4.4 | 4.8 | 5.3 | 4.9 |
| Cl (mEq/liter) | 117 | 106 | 120 | 119 | 121 | 117 | 118 | 116 | 120 | 122 | 120 | 120 |

* Control burned mice, ** Burned mice + *L. casei* (n=7).

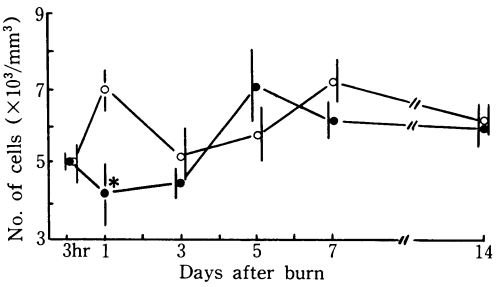


**Fig. 2.** Changes in the number of WBC in normal and burned mice.

Burned mice were prepared as described in the text. At indicated intervals, mice were anesthetized with ether and the number of WBC in normal (○) and burned (●) mice was counted. Bar: mean ± S.E. (n=7), * $p<0.05$.

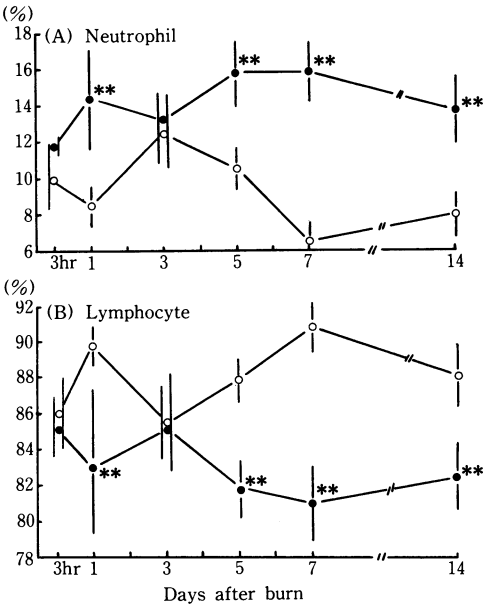


**Fig. 3.** Changes in population of neutrophils and lymphocytes in normal and burned mice.

At indicated intervals, percentages of neutrophils (A) and lymphocytes (B) in normal (○) and burned (●) mice were determined. Bar: mean ± S.E. (n=7), ** $p<0.01$.

els in normal mice for 14 days after the burn (Fig. 3-B). GOT activity markedly increased 3 hr after the burn (269 IU; controls, 83 IU), gradually decreased thereafter and reached nearly the same levels of that in normal mice 14 days after the burn (60 IU; controls, 83 IU). GPT activity in burned mice also increased 3 hr after the burn (202 IU; controls, 23 IU), but drastically decreased one day after the burn and reverted to the normal levels thereafter (Table 3). It has been reported that the neutrophil ratio and GOT and/or GPT activities markedly increased, whereas the lymphocyte ratio decreased in an early period in patients with full thickness burn[1,4,9,14].

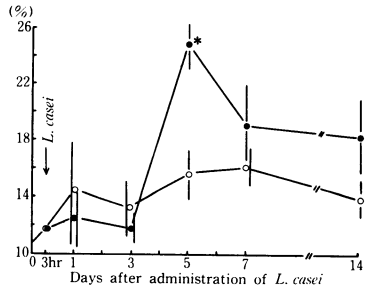


**Fig. 4.** Changes in the population of neutrophils in burned mice pretreated subcutaneously with viable *L. casei* cells.

Burned mice were injected subcutaneously with (●) or without (○) viable *L. casei* cells ($1 \times 10^9$) 3 hr after the burn. At indicated intervals, the percentage of neutrophils was determined. Bar: mean ± S.E. (n=7), ** $p<0.01$.

When burned mice were given viable *L. casei* cells ($10^9$) subcutaneously, various hematological and blood chemical values in *L. casei*-administered burned mice did not differ from those in the untreated burned mice, except for neutrophil ratio (Table 4). As also shown in Table 4, the number of WBC in *L. casei*-administered burned mice was slightly higher than that in untreated burned mice, with no statistical differences throughout the entire experiment.

In summary, no remarkable alterations in hematology and blood chemistry in normal and burned mice occurred after the intraperitoneal or subcutaneous administration of viable *L. casei* cells. Therefore, the toxicity of *L. casei* cells in mice may be low.

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