

Bundled Strategies Against Infection After Liver Transplantation: Lessons From Multidrug-Resistant *Pseudomonas aeruginosa*

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Infection is a life-threatening complication after liver transplantation (LT). A recent outbreak of multidrug-resistant *Pseudomonas aeruginosa* triggered changes in our infection control measures. This study investigated the usefulness of our bundled interventions against postoperative infection after LT. This before-and-after analysis enrolled 130 patients who underwent living donor or deceased donor LT between January 2011 and October 2014. We initiated 3 measures after January 2013: (1) we required LT candidates to be able to walk independently; (2) we increased the hand hygiene compliance rate and contact precautions; and (3) we introduced procalcitonin (PCT) measurement for a more precise determination of empirical antimicrobial treatment. We compared factors affecting the emergence of drug-resistant microorganisms, such as the duration of antimicrobial and carbapenem therapy and hospital stay, and outcomes such as bacteremia and death from infection between before (n = 77) and after (n = 53) the LT suspension period. The utility of PCT measurement was also evaluated. Patients' backgrounds were not significantly different before and after the protocol revision. Incidence of bacteremia (44% versus 25%; $P = 0.02$), detection rate of multiple bacteria (18% versus 4%; $P = 0.01$), and deaths from infections (12% versus 2%; $P = 0.04$) significantly decreased after the protocol revision. Duration of antibiotic (42.3 versus 25.1 days; $P = 0.002$) and carbapenem administration (15.1 versus 5.2 days; $P < 0.001$) and the length of postoperative hospital stay (85.4 versus 63.5 days; $P = 0.048$) also decreased after the protocol revision. PCT mean values were significantly higher in the bacteremia group (10.10 ng/mL), compared with the uneventful group (0.65 ng/mL; $P = 0.002$) and rejection group (2.30 ng/mL; $P = 0.02$). One-year overall survival after LT significantly increased in the latter period (71% versus 94%; $P = 0.001$). In conclusion, the bundled interventions were useful in preventing infections and lengthening overall survival after LT.

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Abbreviations: HCC, hepatocellular carcinoma; ICT, infection control team; LDLT, living donor liver transplantation; LT, liver transplantation; MDRP, multidrug-resistant *Pseudomonas aeruginosa*; MELD, Model for End-Stage Liver Disease; PBC, primary biliary cirrhosis; PCT, procalcitonin; PSC, primary sclerosing cholangitis.

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Although liver transplantation (LT) is the only definitive treatment for patients with end-stage liver disease, it has been one of the most difficult treatments compared with other types of abdominal surgery.⁽¹⁻³⁾ The most common cause of in-hospital mortality after LT is infection, accounting for 62.5% of all causes.⁽¹⁾ Candidates for LT are usually at an extremely high risk for infection because of preoperative protein-energy malnutrition caused by long-term cirrhosis.⁽⁴⁾ In addition, postoperative immunosuppressants are essential for preventing rejection. Therefore, overcoming infectious complications is vitally important for optimal patient outcomes after LT.

In 2012, our hospital experienced an outbreak of multidrug-resistant *Pseudomonas aeruginosa* (MDRP) that was resistant to fluoroquinolone, aminoglycoside, and carbapenem. In particular, 3 patients became carriers after LT and 2 of them died from uncontrolled pneumonia and abdominal sepsis. Furthermore, MDRP detected from these patients showed the identical genotype. This circumstance is generally considered to be the product of an inappropriate use of antibiotics and insufficient hand hygiene practices and contact precautions. Subsequently, we suspended the performance of adult LT for a period to eliminate MDRP and to launch a protocol for controlling infectious complications. We introduced 3 measures to successfully restart performing LTs. First, we added a requirement for LT candidates to be able to walk independently at the time of their admission and operation. Second, we established practical contact precautions which were continuously evaluated through direct audits by our hospital's infection control team (ICT). Third, we introduced procalcitonin (PCT) monitoring for clinical decision-making regarding starting or stopping antimicrobials in LT recipients.

Patients with cirrhosis often experience muscular depletion, or sarcopenia, as a consequence of protein-energy malnutrition. Recently, some investigators demonstrated the significance of sarcopenia on the prognosis after LT.^(5,6) In addition, sarcopenia has been shown to be strongly correlated with severe infectious complications after LT.^(7,8) However, the scoring systems such as the Child-Pugh classification or the Model for End-Stage Liver Disease (MELD) score do not address sarcopenia. In accordance with the accumulating evidence, we added as a requirement for acceptance for LT the ability to walk independently as a surrogate indicator of the patient not being severely sarcopenic.

Hand hygiene practices and contact precautions are primitive but critical measures to avoid nosocomial

transmission of microorganisms.⁽⁹⁾ Although their significance seems to be recognized conceptually, we had overlooked their effects, resulting in the neglect of nosocomial spread of MDRP in the transplant ward. We established credible criteria for hand hygiene practices and contact precautions, together with an objective monitoring system to improve compliance.

In transplant medicine, differentiation of systemic infection from rejection after LT is sometimes difficult because of their similar symptoms. Kaido et al.⁽¹⁰⁾ recently reported the usefulness of PCT in predicting bacteremia after LT. Accordingly, we introduced PCT monitoring in LT recipients to effectively differentiate their condition to avoid the futile use of antimicrobials as much as possible.

In the present study, we investigated the effectiveness of our bundled interventions against postoperative infection in patients undergoing LT.

Patients and Methods

The 130 consecutive adult patients who underwent living donor liver transplantation (LDLT) or deceased donor liver transplantation at Kyoto University Hospital (Kyoto, Japan) between January 2011 and October 2014 were enrolled in the study. Because of the prevalence of MDRP, a 4-month suspension period of LT was instituted from September to December in 2012 (Fig. 1). The study patients were divided into 2 groups: group A (n = 77) was composed of patients before the start of the suspension period, and group B (n = 53) was composed of patients after the suspension period. We introduced 3 measures that are explained in detail below as a bundle of integrated measures in group B. The patients' demographic and clinical data were all extracted from their medical records. The study was approved by the ethics committee of Kyoto University and conducted in accordance with the Declaration of Helsinki of 2008.

SURGICAL PROCEDURES AND PERIOPERATIVE MANAGEMENT

The surgical techniques of LT have been described in detail elsewhere.^(11,12) The method for wound closure was not changed between the 2 groups. At the time of operation, we routinely inserted a 7-Fr tube as a jejunostomy for enteral nutrition in the proximal jejunum.⁽¹³⁻¹⁵⁾ Surgeon experience did not differ between groups A and B. The residents were taught to perform hand hygiene and contact precautions (see below) by

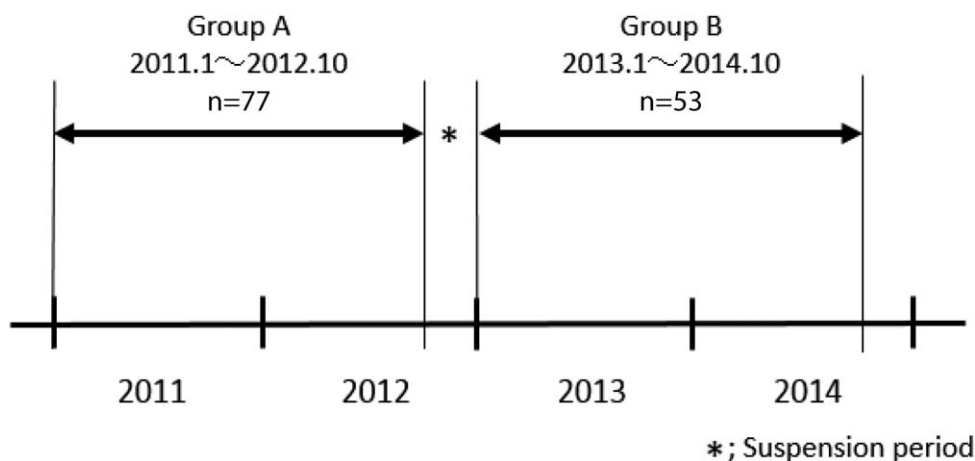


FIG. 1. Illustration of the study period. LT was suspended in our hospital between September and December in 2012, as indicated by an asterisk.

the ICT and senior surgeons when they rotated to our department, and they were monitored in the same way as the people attending the surgery.

Prophylactic antibiotics such as ampicillin (1 g) and cefotaxime (1 g) were administered intravenously 30 minutes before and every 3 hours during the operation. These agents were continued every 8 hours for 3 days after LT.

Immunosuppressants, consisting of tacrolimus or cyclosporine and mycophenolate mofetil in addition to low-dose steroids, were started within 24 hours after LT in all patients. In ABO-incompatible cases, the recipients were administered rituximab (300 mg) more than 2 weeks before LT and received mycophenolate mofetil preoperatively.⁽¹⁶⁾ Plasma exchange was additionally performed if the titer of anti-A or anti-B antibody did not decrease after rituximab treatment, aiming for immunoglobulin M and immunoglobulin G titers below 1:16.⁽¹⁶⁾

Preoperative nutritional therapy has been described in detail elsewhere.⁽⁵⁾ Briefly, supplements containing rich branched-chain amino acids, zinc, dietary fiber, and oligosaccharides were administered 3 times a day for approximately 2 weeks before LDLT. Patients also took a *Lactobacillus* preparation as a symbiotic once a day for the same period. These agents were continued after the operation via jejunostomy or orally until the patient was discharged. Postoperative enteral nutrition was started within 24 hours after LT via tube jejunostomy and continued until the patient could take adequate food orally. Oral intake was usually started around postoperative day 5 if the patient could swallow without aspiration. Importantly, in all patients in group B, dietitians adjusted the

nutritional composition for each patient to fulfill the guidelines of the European Society of Parenteral and Enteral Nutrition.⁽¹⁷⁾

FIRST MEASURE: ADDITIONAL REQUIREMENT FOR PROSPECTIVE LIVER RECIPIENTS TO BE WITHOUT SEVERE SARCOPENIA

Before the LT suspension period, we accepted patients with cirrhosis for LT according to scoring systems such as the Child-Pugh classification or the MELD score, without taking the patient's nutritive status into consideration.⁽¹⁸⁾ We added a requirement for acceptance for LT the ability to walk independently as a surrogate indicator of the patient not being severely sarcopenic. Patients who could not walk alone were diagnosed as severely sarcopenic and were not eligible for LT. Those patients underwent intensive rehabilitation with the goal of becoming able to walk independently.

The ability to walk was assessed at the time of transplantation as well as at the time of admission. If a patient could not ambulate after admission because of the progression of sarcopenia, LT was postponed until the patient could walk alone through the intervention of rehabilitation therapy. If a patient could not ambulate after admission due to the progression of primary liver diseases, such as rupture of esophageal varices or hepatic coma, then LT was postponed until the patient could walk alone by therapeutic intervention. We did

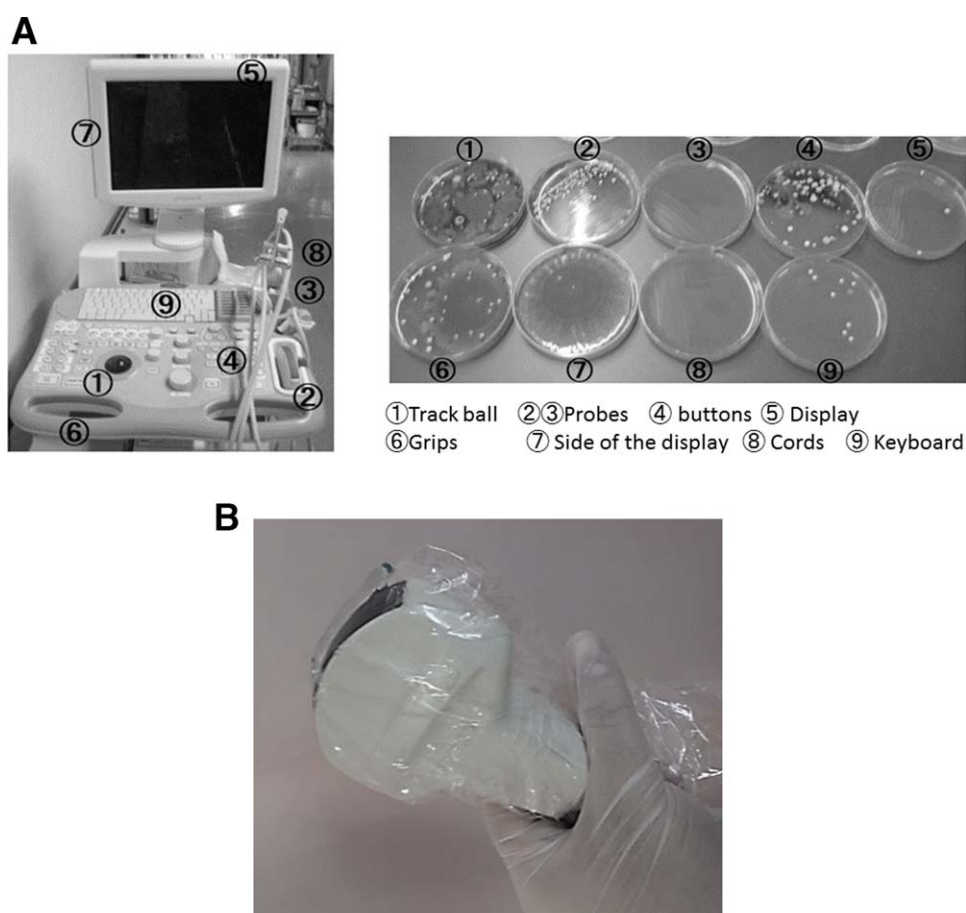


FIG. 2. The abdominal ultrasonography device was found to be highly contaminated with bacteria. (A) Results of microbiological analysis. (B) A protocol was initiated to cover the probe and hands when performing ultrasonography, according to the results of (A).

not establish any particular rule about the distance that a patient was required to walk alone. Patients who could not walk without using an assistive device like a walker or cane were not allowed to be candidates for transplantation.

SECOND MEASURE: IMPROVEMENT IN HAND HYGIENE PRACTICES AND CONTACT PRECAUTIONS

In order to prevent nosocomial transmission, we were thoroughly educated by the ICT of our hospital to carefully perform hand hygiene at the required times. All staff in our department began to carry a portable bottle of hand disinfectant and were instructed to perform hand hygiene whenever they entered or exited each patient's area. Additionally, all staff in our ward made it a rule not to wear a watch on their arm because

we considered the possibility that microorganisms might be horizontally transferred by it. The sleeves of the doctors' white coats had to be rolled up in order to perform hand hygiene easily to the level of the wrists. Compliance with the hand hygiene protocol was monitored through direct audits by the ICT members, and we received feedback on the results every 3 months. The ICT consisted of specialists in infectious disease who were independent from our department and who function as auditors and consultants to the surgeons.

Through investigations after the outbreak of MDRP, we found that the ultrasonography devices were highly contaminated with bacteria (Fig. 2A). This contamination was thought to be one of the modes of transmission because we usually perform abdominal ultrasound at least twice a day in the first week after LT to check the hepatic blood flow. (Subsequently, we perform it according to the patient's status.) Therefore, we instituted a protocol to wash our hands, to wear disposable gloves, to cover the

ultrasound probes with a disposable plastic bag, and to change the gloves and bags each time the device was used (Fig. 2B).

All categories of hospital care providers, including physiotherapists and dietitians, were monitored for their compliance with hand hygiene in the same way. The relevant staff members were restricted to a small number of people, so they were told immediately if they had not performed proper hand hygiene. Patients' families and visitors were educated on the method of hand hygiene when they first visited our ward.

THIRD MEASURE: INDUCTION OF PCT MONITORING FOR DECISION-MAKING REGARDING EMPIRICAL ANTIMICROBIAL TREATMENT

For the purpose of a precise diagnosis of systemic infections and differentiation of rejection from systemic infection, we introduced sequential measurement of serum PCT after LT in group B. Overall levels and fluctuations of PCT acted as indicators of infection and were used for diagnosis along with physical examinations and other laboratory test results.

At first, as a validation of a previous study,⁽¹⁰⁾ we performed prospective analysis to confirm the usefulness of our decision-making algorithm based on PCT levels in group B. PCT was measured on day 2 or 3, and then on days 5, 7, 10, 14, 21, and 28 after LT; additional measurements were taken when patients experienced a fever higher than 38°C. PCT levels were measured using the Brahms PCT luminescence immune assay from Roche Diagnostics K.K. (Tokyo, Japan), and the results were returned in approximately 2 hours. Patients with PCT levels >2.0 ng/mL were considered to have bacteremia, and empiric therapy with antimicrobials was started immediately. Antibiotics used for the empiric therapy were carbapenem, piperacillin/tazobactam, or cefepime hydrochloride. We routinely measure the serum concentration of immunosuppressants. Usually, we set target trough levels of tacrolimus and cyclosporine at 10–15 ng/mL and 100–150 ng/mL in the early phase after the transplant operation. When the patient's PCTs exceeded 2.0 ng/mL and symptoms of infection were observed, we lowered the trough levels of these immunosuppressants.

Patients with PCT levels <0.5 ng/mL were diagnosed as not having bacteremia, and immunosuppression was not stopped. In patients with PCT levels

between 0.5 and 2.0 ng/mL, we decided on treatment while taking into consideration other signs including white blood cells, C-reactive protein, and liver enzymes. When the PCT values after the start of empirical antimicrobial therapy began to decrease, we considered the choice of drugs to be appropriate. When the clinical symptoms or laboratory data indicating infection such as C-reactive protein or white blood cell counts improved, we changed the antibiotic(s) to a narrow-spectrum antibiotic according to the antimicrobial susceptibility test or we stopped the antibiotic treatment.

The patients in group B were divided into 3 groups: uneventful group, rejection group, and bacteremia group. Patients who experienced both rejection and bacteremia were considered as belonging to the bacteremia group. We compared values of PCT after LT between these 3 groups. A previous study revealed that the PCT values in patients without bacteremia stabilizes to a normal level on and after the seventh day after LT.⁽¹⁰⁾ Thus, in the uneventful group, we used maximum values on more than 7 days after LT, whereas we analyzed values on febrile events in the other 2 groups. Diagnoses of rejection were made by pathologists based on liver biopsy.

OTHER CHANGES LAUNCHED AFTER THE OUTBREAK OF MDRP

In order to prevent horizontal spread of MDRP, patients who were infected were each transferred into their own single room, and the remaining rooms were thoroughly cleaned by the professional cleaning staff. When health care providers went into a patient's room, they were required to wear a disposable apron, a mask, and gloves in addition to performing hand hygiene. Conversely, when the patients went out from their rooms, they had to perform hand hygiene and wear a mask on their mouth. These rigorous rules for contact precautions were continued in group B if the patient was infected with microorganisms such as multidrug-resistant *Staphylococcus aureus*.

Additionally, we remodeled the care units to provide ample workspace and to facilitate no-touch access to each sanitary room.

INTEGRATED ANALYSIS

Outcomes that were considered to be related to infectious complications and drug resistance of microorganisms were established and compared between groups A and B according to the following factors:

TABLE 1. Comparison of Patients' Demographic Characteristics Between Group A (Before the LT Suspension Period) and Group B (After the LT Suspension Period)

	Group A (n = 77)	Group B (n = 53)	P Value
Age, years	51 (19-69)	54 (21-68)	0.24
Sex			0.21
Male	36	31	
Female	41	22	
Living/deceased donor	71/6	49/4	0.76
ABO compatibility			0.32
Identical	41	25	
Compatible	15	22	
Incompatible	21	6	
Child-Pugh score	10 (5-14)	10 (5-15)	0.79
MELD score	18 (6-40)	17 (6-27)	0.15
Liver disease, n			0.88
Hepatitis B or C	16	11	
PBC or PSC	18	15	
HCC	15	11	
Others	28	16	

NOTE: Continuous variables are indicated as median (range).

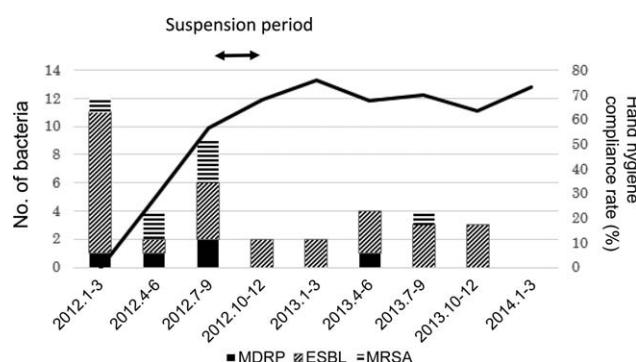


FIG. 3. Relationship between the occurrence of drug-resistant microorganisms and hand hygiene compliance rate. The incidence of drug-resistant bacteria was inversely correlated with the hand hygiene compliance rate.

frequency of bacteremia, number of deaths related to infection, duration of hospital stay, duration of administration of antibiotics and carbapenem, and 1-year survival after LT. The species of the bacteria that were detected by blood culture were also evaluated.

STATISTICAL ANALYSIS

Continuous variables were indicated by median (range). Comparisons were made with mean values by the Mann-Whitney U test or the chi-square test when

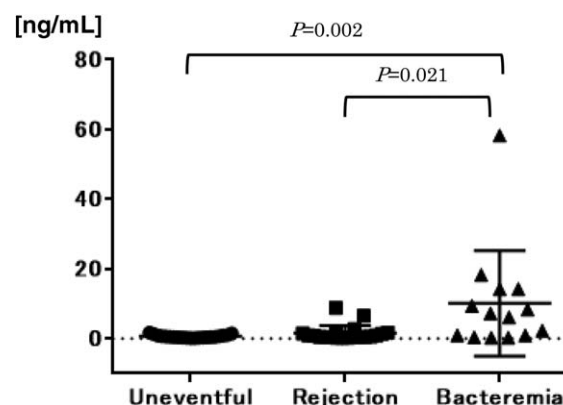


FIG. 4. Comparison of maximum PCT values among the uneventful, rejection, and bacteremia groups in the latter half of the study period.

appropriate using JMP 5.0 (SAS Institute, Cary, NC). Overall survival rates were calculated and analyzed by the Kaplan-Meier method and the log-rank test. Values of $P < 0.05$ were considered statistically significant.

Results

PATIENT CHARACTERISTICS

Descriptive statistics of the study population ($n = 130$) are shown in Table 1. Patient age, sex, ABO compatibility, underlying liver disease, Child-Pugh score, and MELD score were not significantly different between the patient groups.

COMPLIANCE WITH STANDARD PRECAUTIONS AND HAND HYGIENE

The initial direct audit by the ICT found compliance with hand hygiene to be $<40\%$ among the nurses in our ward, and the compliance of the doctors was much lower. After repeated education and feedback from the ICT audit during the LT suspension period, compliance gradually but remarkably rose (Fig. 3). Importantly, the frequency of detection of multidrug-resistant microorganisms such as multidrug-resistant *Staphylococcus aureus*, extended spectrum β -lactamase-producing microorganisms, and MDRP from the patients in our ward was inversely correlated with the compliance rate. Abdominal ultrasounds were performed perfectly with respect to adherence to the

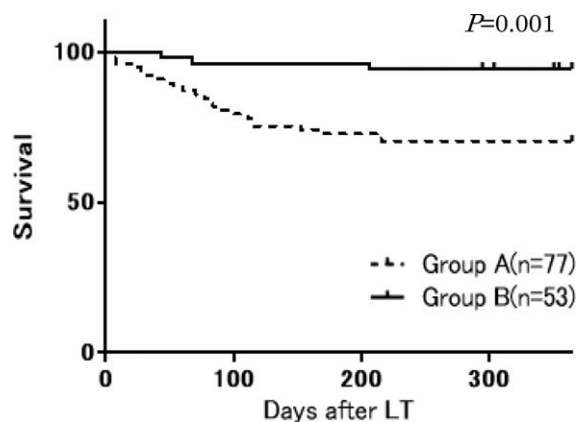


FIG. 5. Kaplan-Meier analysis comparing acute-phase (1-year) survival rate between group A and group B. The survival rate significantly improved after the LT suspension period (71% versus 94%; $P = 0.001$).

protocol mentioned above, and compliance with the protocol was continually checked among the members of our department or by the ICT audit. As an educational program, monthly repeated lectures by the ICT in the multidisciplinary conference and feedback on the results of monitoring with notices about contact precautions were considered likely to be effective.

PROSPECTIVE ANALYSIS OF PCT

In group B, 21 patients including 1 patient who underwent retransplantation experienced neither rejection nor bacteremia during the study period (the uneventful group). In the remaining 32 patients, there were 20 events of acute cellular or antibody-mediated rejection and 14 events of bacteremia. The PCT values were compared among the 3 groups (Fig. 4). The average PCT value in the bacteremia group (10.10 ng/mL) was significantly higher than in the uneventful group (0.65 ng/mL; $P = 0.002$) and the rejection group (2.30 ng/mL; $P = 0.02$), indicating that PCT could be an effective indicator for the detection of systemic infection.

The cutoff value determined by a previous study was also evaluated.⁽¹⁰⁾ If the PCT value was set to 0.5 ng/mL for the diagnosis of bacteremia, the sensitivity and specificity would be 79% and 45%, respectively. Alternatively, for a PCT value of 2.0 ng/mL, the sensitivity and specificity would be 64% and 93%. When we set the cutoff value of PCT at 2.0 ng/mL, the positive and negative predictive values were 75% and 88%, whereas

at 0.5 ng/mL, these values were 32% and 86%, respectively.

INTEGRATED ANALYSIS

The 1-year survival rate after LT was significantly improved in group B (Fig. 5, group A versus group B = 71% versus 94%; $P = 0.001$). Length of postoperative hospital stay (85.4 versus 63.5 days; $P = 0.048$), use of antimicrobials (42.3 versus 25.1 days; $P = 0.002$), and carbapenem administration (15.1 versus 5.2 days; $P < 0.001$) were significantly decreased in group B (Table 2). Additionally, the frequency of bacteremia (44% versus 26%; $P = 0.03$), number of times multiple species of microorganisms were detected in blood culture (18% versus 4%; $P = 0.01$), and deaths related to infections (12% versus 2%; $P = 0.04$) were also significantly improved. Although the total number of bacteria detected from blood culture was reduced (group A versus group B = 47 versus 17), the percentages of species was much the same in terms of the high frequency of *Enterobacteriaceae* (group A versus group B = 55% versus 58%). In both groups, the most common species of bacteria isolated from the blood culture was *Enterococcus faecium*.

Discussion

The present study represents a superb effect of launching bundled interventions as we recognized the emergence of MDRP as a turning point in the care of our LT patients. Although our strategy was an integration of basic measures, the new infection control protocol improved not only factors associated with the expansion of drug-resistant microorganisms, but also greatly improved the morbidity from bacteremia and short-term mortality after LT. The devastating experience of MDRP in our patients helped us to re-realize the importance of controlling infection, resulting in the achievement of much better outcomes after LT. From the viewpoint of medical economics, our bundled interventions reduced expenses with respect to futile admission for LT, futile administration of antibiotics, and decreased number of posttransplant hospital days. In addition, the present study can be used as evidence of the importance of contact precautions for health care providers.

Since January 2013, we restricted acceptance for LT to patients who can walk independently, setting a value on patients' muscular status. In general, the MELD score has been used as a criterion for liver allocation

TABLE 2. Comparison Between Groups Regarding Prognosis and Parameters Related to Infection

	Group A (n = 77)	Group B (n = 53)	P Value
Death within 1 year, n (%)	22 (29)	3 (6)	0.001
Death due to infection, n (%)	9 (12)	1 (2)	0.04
Bacteremia, n (%)	34 (44)	14 (26)	0.03
Detection of multiple bacteria strains, n (%)	14 (18)	2 (4)	0.01
Postoperative hospital length of stay, days	85.4	63.5	0.048
Duration of antibiotic administration, days	42.3	25.1	0.002
Duration of carbapenem administration, days	15.1	5.2	<0.001

worldwide. However, this scoring system has been pointed out to have some limitations in predicting prognosis because it does not cover some cirrhotic complications such as hepatic encephalopathy, spontaneous bacterial peritonitis, and bleeding esophageal varices.⁽¹⁹⁾ Moreover, accumulating evidence has demonstrated recently the importance of sarcopenia in the prognosis of LT.⁽⁵⁻⁸⁾ Therefore, we considered that outcomes after LT could be improved if we took muscular status into consideration when evaluating patients for LT. To avoid futile transplantation resulting in the recipient's death or the emergence of drug-resistant bacteria, we decided to add a new indication regarding sarcopenia for LT. This new indication might be a link to the appropriate allocation of liver grafts and economic savings through avoiding prolonged antibiotic therapy.

Currently, hand hygiene is widely recognized as a basic measure to reduce the incidence of hospital-acquired infections.⁽²⁰⁾ After the World Health Organization Global Patient Safety Challenge was launched in 2005 with the aim of reducing health care-associated infections worldwide,⁽²¹⁾ some investigators demonstrated the effectiveness of compliance in reducing the number of infections.^(22,23) However, achieving high compliance in hand hygiene is still not straightforward. Therefore, we created a monitoring system in which the ICT directly audits the compliance of hand hygiene and provides feedback at fixed intervals. Recently, a pilot study using an electronic monitoring system found that hand hygiene compliance was elevated.⁽²⁴⁾ However, we were able to prove effectiveness by direct observation. The findings of the present study might be helpful in educating medical staff who provide care to immune-compromised patients.

We also introduced an easy protocol to prevent contamination of ultrasound devices to avoid these devices

being possible transmission vectors. This method was also easy to apply because of its clarity and low expense.

We established innovative sequential PCT monitoring in managing infection after LT. PCT is a biomarker first described in 1993 by Assicot et al.⁽²⁵⁾ as a useful indicator in diagnosing bacterial infection. Several studies have revealed the effectiveness of sequential PCT monitoring in various situations to achieve prompt diagnosis and treatment.⁽²⁶⁻³⁰⁾ In the setting of solid organ transplantation, the use of PCT in differentiating infection from rejection has been difficult; sometimes these complications present with the same symptoms, but the management of each entity is the opposite. Although some investigators have attempted to demonstrate the usefulness of PCT monitoring, these studies were performed with a small sample size, and the evidence in LT is inadequate.⁽³¹⁻³³⁾ The present study showed significant differences in the results of serum PCT, not only between the bacteremia group of patients and the uneventful group, but also between the bacteremia group and the rejection group in a prospective setting.

In the analysis of PCT, we found a few outliers: 3 patients in the rejection group presented with high values exceeding 2.0 ng/mL, and another 5 patients in the bacteremia group had results lower than 2.0 ng/mL. The outliers in the rejection group had local infections such as abdominal abscess and cholangitis. For these patients, applying antimicrobials according to the value of PCT as an indicator for detecting infection is considered to be permissible because each of these infections is sometimes lethal. The reason for the existence of outliers in the bacteremia group might be because the timing of drawing blood had been too early. It has been stated that the lag time for PCT induction is approximately 2-4 hours, with peak levels occurring at 24-48 hours after sepsis.⁽³⁴⁾ It seems that there might be some differences between individuals regarding the timing of PCT induction, but more cases need to be accumulated and analyzed to reveal the mechanisms of the gap. In view of this circumstance, it is recommended to diagnose bacteremia by employing PCT as one of the significant signs of severe infection.

In our microbiological analysis, we revealed that the majority of cases of bacteremia were caused by *Enterobacteriaceae* in both group A and group B after the LT suspension period. Patients with cirrhosis are usually at high risk of bacterial translocation.⁽³⁵⁾ Under this circumstance, we routinely use probiotics and tube jejunostomy in order to maintain intestinal flora.

However, our data suggest that there is some room for improvement in the menu and protocol of nutrient therapy.

In the present study, the hospital length of stay of the patients in our series was over 85 days in the preintervention group and over 60 days even in the postintervention group. Furthermore, the duration of antibiotic therapy in the postintervention group was over 25 days. These indicators seemed to be significantly longer than those of other studies.⁽³⁶⁻³⁹⁾ One possible explanation for this is the unique Japanese insurance system, which covers almost all costs related to LT. Japanese patients tend to stay longer in the hospital than in other countries, and adjustments in immunosuppressive medication and rehabilitation are performed during the same hospitalization period for LT. Understandably, these circumstances result in greater opportunities for patients to become infected and require antibiotic administration. Once a patient is diagnosed with bacteremia, we use antibiotics for at least 14 days according to the Japanese guideline.⁽⁴⁰⁾ However, we would like to shorten the duration of antimicrobial administration because we consider that administration for over 25 days in the postintervention group is still very high.

The present study had several limitations. First, we cannot exclude some other possible factors that might have affected the study population because of the inherent characteristics of historical cohort design. However, we were able to minimize the risks of some biases because the patient backgrounds between the 2 groups were not significantly different. Second, we could not assess the individual contribution of each infection control measure in the improvement of the infectious prognosis. Third, in the analysis of PCT, the sample size of each group was limited. That is, the sensitivity of the cutoff of 0.5 ng/mL and the specificity of 2.0 ng/mL in detecting bacteremia were lower than in the previous report.⁽¹⁰⁾ Even though we could validate the same tendency with the previous study and despite the reliability of the PCT value, the treatment decision for antibiotic therapy should be made according to multiple sources of information. The improved outcomes we present here from the present study are the products of several confounding factors. However, we believe this report provides significant insights into how to prevent the emergence and spread of drug-resistant microorganisms which cannot be conquered by current antibiotics, especially from the viewpoint of education and medical economy related to transplant medicine. The use of these bundled interventions

would be beneficial in the setting of high rates of postoperative infection or an outbreak setting. Further investigations in larger and multicenter settings are needed to evaluate the usefulness of their routine use in posttransplant care.

In conclusion, our bundled interventions against postoperative infection were useful for suppressing infectious complications and for improving overall survival after LT.

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