Importance of Controlling Drug-resistant *Pseudomonas aeruginosa* Infection: Experience from Lung Transplantation in a Cystic Fibrosis Case

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**Abstract**

Cystic fibrosis (CF) is rare in Japan. We encountered a CF case with drug-resistant *Pseudomonas aeruginosa* infection and successfully performed lung transplant from living related donors. A combination of beta-lactams and aminoglycosides for drug-resistant *P. aeruginosa* infection was administered before lung transplantation. Intravenous colistin was also used immediately before and after transplant surgery. Gram staining of respiratory specimens was performed every day after surgery and it was useful in monitoring infection status. Strict monitoring of infections by the Gram staining and culture of respiratory specimens is considered to be effective in preventing lower respiratory infection in lung transplantation.

**Key words:** cystic fibrosis, *Pseudomonas aeruginosa*, lung transplantation, ventilator-associated tracheobronchitis

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**Introduction**

Cystic fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane regulator (CFTR) gene, which encodes a chloride channel in epithelial membranes (1). Although CF is a common autosomal recessive disorder in Caucasians, its frequency is very low in Japan (2). As the most common cause of death in CF cases is respiratory failure, lung or heart-lung transplantation is the ultimate treatment option for patients with CF, particularly those with end-stage lung damage. Here, we report for the first time a CF case with drug-resistant *Pseudomonas aeruginosa* infection that was successfully treated by a lung transplant from living related donors in Japan, and describe in detail how we controlled drug-resistant *P. aeruginosa* infection before and after lung transplant surgery.

**Case Report**

A 24-year-old male with dyspnea on effort, productive cough and fever was diagnosed as having CF with chronic sinusitis at the age of 15 years. He was the second child of non-consanguineous parents and his mother had systemic lupus erythematosus and Graves’ disease. His past medical history revealed pseudo-Bartter syndrome and cholangiitis. Missense mutation Q98R was detected in exon 4 and polymorphic 125C was present in exon 1 on CFTR mutation screening, and sweat chloride concentration was 330 mmol/L (normal range: 0-40 mmol/L), thus confirming CF.

On the day before surgery, his vital signs were as follows: body temperature, 37.5°C; heart rate, 124 beats/minute with
Blood gas analysis indicated a pH of 7.378, PCO2 of 62.6 torr, PO2 of 78.2 torr, and HCO3 of 36.0 mmol/L under 3 L/min O2 nasal inhalation. On physical examination, he was emaciated and coarse crackles were heard in the whole lung, and no signs of systemic lymphadenopathy, hepatosplenomegaly, or pre-tibial edema were noted. Laboratory findings on the day before surgery were: WBC, 7,600/mm³; (Seg, 71%; Lym, 19%; Mono, 5%; Eo, 4%; Ba, 1%); RBC, 4.59×10¹²/mm³; Hb, 11.8 g/dL; Ht, 40.7%; Plt, 19.3×10¹²/mm³; CRP, 1.01 mg/dL; TP, 8.1 mg/dL; Alb, 3.8 mg/dL; γGTP, 141 IU/L; ALP, 749 IU/L; LDH, 168 IU/L; BUN, 11.0 mg/dL; Cr, 0.55 mg/dL; Na, 138 mEq/L; K, 3.6 mEq/L; and Cl, 95 mEq/L.

After a diagnosis of CF at age 15 years, macrolide therapy was initiated. *Staphylococcus aureus* was initially detected at 3 years after CF diagnosis and cefazolin was routinely used during exacerbation, and was effective. The frequency of exacerbation increased gradually during the clinical course and *S. aureus* was replaced by *P. aeruginosa*, and was continuously detected during exacerbation of chronic respiratory infection (Fig. 2). Drug susceptibility tests for *P. aeruginosa* indicated that it was gradually becoming resistant to beta-lactam, quinolone and aminoglycoside antibiotics. After 60 admissions due to exacerbation of chronic airway tract infection, severe respiratory failure, and poor general condition, lung transplantation from living relatives was planned. As control of the airway tract infection, severe respiratory failure, and poor general condition, lung transplantation from living relatives was planned. As control of the pulmonary function test data were as follows: VC, 1.33 L; %VC, 33.1%; FEV₁, 0.83 L; %FEV₁, 22.1%; and FEV₁/FVC, 61.0%. These data indicated both severe obstructive and restrictive dysfunction. Microbiological tests revealed *P. aeruginosa* at 1×10⁷ CFU/mL in sputum and the minimum inhibitory concentrations (MICs) for piperacillin (PIPC), amikacin (AMK), gentamycin (GM), imipenem and cilastatin (IPM/CS) and ciprofloxacin (CPFX) were ≥32, 16, 16, ≥32, and 8.0 μg/mL, respectively, which did not fully satisfy the criteria for multdrug-resistant *Pseudomonas* (MDRP; requires MICs for AMK, IPM/CS and CPFX of ≥32, ≥16, and ≥4 μg/mL, respectively). *P. aeruginosa* was also detected in the paranasal sinus at 2×10⁶ CFU/mL and the MICs for GM, IPM/CS and CPFX were 2.0, <0.5, and 8.0 μg/mL, respectively. Chest x-ray films before lung transplant surgery indicated diffuse bilateral cystic and bronchiectatic changes (Fig. 1a). Chest computed tomography showed progressive cystic and bronchiectatic changes in both lungs (Fig. 1b, 1c).

As *S. aureus* was also isolated with *P. aeruginosa*, a combination of AZT and arbekacin (ABK) was administered after admission. Although *S. aureus* was found to be methicillin sensitive after several days of isolation, ABK was continued because it was potentially effective for *P. aeruginosa*. The triple regimen of AZT, AMK and rifampicin (RFP) was administered for exacerbation that occurred 3 months before surgery.
### Discussion

CF is a fatal autosomal recessive hereditary disease with an incidence in Caucasian populations of around 1 in 2,500 (1). In contrast, the incidence of CF in Japan is extremely low; it is estimated to be 1 in 350,000 (2). To date, a total of approximately 150 cases have been reported in Japan. The cause of death in CF cases is typically lung diseases due to respiratory failure. In recent years, aggressive management of lung disease in CF has resulted in great im-

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**Figure 2.** Clinical course from the year of diagnosis to lung transplantation surgery.

<table>
<thead>
<tr>
<th>Year</th>
<th>Sputum Culture</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>S. aureus (MSSA)</td>
<td>inhaled Tobramycin</td>
</tr>
<tr>
<td>16</td>
<td>H. influenzae</td>
<td>Clarithromycin 200mg</td>
</tr>
<tr>
<td>17</td>
<td>P. aeruginosa</td>
<td>Azithromycin 250-750 mg/w</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>Cefazolin 2-6 g</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td>Tazobactam/Piperacillin 5 g</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>Aztreonam 4 g</td>
</tr>
<tr>
<td>21</td>
<td></td>
<td>Arbekacin 200mg</td>
</tr>
<tr>
<td>22</td>
<td></td>
<td>300mg</td>
</tr>
<tr>
<td>23</td>
<td></td>
<td></td>
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<tr>
<td>24</td>
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</tbody>
</table>

(years old)
provements in length and quality of life, and the median expected survival age has reached 36 years (4).

We recently reported three CF cases with confirmed CFTR mutations in Nagasaki, Japan (5). The case described in this report has the longest follow-up period of these cases. The respiratory failure progressed gradually over the last 10 years, and several factors and conditions, such as FEV1 below 30% of predicted FEV1, oxygen-dependent respiratory failure, hypercapnia, and pulmonary hypertension, fulfilled the indications for lung transplantation (6).

CF patients in advanced stages of lung disease ultimately require lung transplantation; however, drug-resistant P. aeruginosa and other multidrug-resistant pathogens, which are endemic in CF patients with advanced lung disease, make it difficult to successfully manage such patients. The results of our study suggest that P. aeruginosa resistance to colistin is a major concern in CF patients with advanced lung disease. However, there are few reports on multidrug-resistant P. aeruginosa in Japan, and this is the first report of P. aeruginosa resistance to colistin in the world. Our findings suggest that P. aeruginosa resistance to colistin is a major concern in CF patients with advanced lung disease. Therefore, it is important to improve the management of multidrug-resistant P. aeruginosa in CF patients with advanced lung disease.
*P. aeruginosa* infection is a major obstacle to completing lung transplantation (7). Needless to say, control of this infection during the perioperative period is critical to patient outcome. Pre-transplant colonization with MDRP, however, is not a contraindication to transplantation, as it has no significant influence on short-term survival (6). In the present case, *P. aeruginosa* was isolated from about 2 years before surgery, and the drug susceptibility profile of isolates temporarily showed MDRP.

The Cystic Fibrosis Foundation as well as the European Cystic Fibrosis Society strongly recommend the chronic use of inhaled tobramycin to improve lung function and reduce the frequency of exacerbation for patients with CF aged 6 years or older who have moderate to severe lung disease and *P. aeruginosa* persistently present in airway cultures (4, 8). Furthermore, we have previously reported the efficacy of inhaled tobramycin in cases with bronchiectasis (9). Although it is reasonable to begin inhaled treatment when *P. aeruginosa* is isolated, inhalation therapy was not used in this patient because of severe hemoptysis induced by inhaled stimulants, including 0.9% saline.

Antibiotic susceptibility testing is recommended to be repeated at regular intervals while patients are on the waiting list to ensure that a recently tested antibiotic combination is administered at the time of transplant surgery (6). We therefore used the break-point checkerboard plate, developed for screening appropriate antibiotic combinations against drug-resistant organisms, such as MDRP (3). Although the checkerboard plate method has not been standardized in the clinical setting, it is a potentially favorable method to select two antibiotics with maximum efficacy against drug-resistant bacterial infection. We selected a triple regimen of AZT, RFP and AMK, followed by TAZ/PIPC with ISP. These were selected based on the result of checkerboard analysis, while TAZ/PIPC and ISP were used instead of PIPC and AMK. TAZ/PIPC was selected because the dose of PIPC can be increased further than with single administration of PIPC, and ISP was used in order to avoid prolonged exposure to AMK, which may lead to further drug resistance. These treatments were effective and the patient recovered from exacerbation before transplantation. Colistin, a classic polymyxin, was recently applied to treatment of MDRP and other drug-resistant Gram-negative bacteria (10, 11). Although colistin has not yet been approved in Japan, it was used before and after transplant surgery in this case with the approval of both the patient and the Internal Review Committee of Nagasaki University Hospital. We used colistin for only short periods before and after surgery because we wanted to reduce drug-resistant *P. aeruginosa* levels as much as possible while minimizing serious complications due to its toxicity, and to prevent the production of colistin-resistant *P. aeruginosa*. As it was apparent that colistin was unable to completely eliminate all *P. aeruginosa* in the destroyed lung, lung transplantation was the only option for ultimately eliminating drug-resistant *P. aeruginosa*. The first priority before surgery in this case was for the patient to receive surgery without unexpected complications or conditions. Longer usage of colistin may cause severe adverse effects, such as impaired kidney and central nervous function, and such effects would have delayed the surgery. All approaches were effective and no severe exacerbation was observed for a month before transplant surgery, and the surgery was performed as scheduled.

Another important aspect of this case was that *P. aeruginosa* colonizing the paranasal cavity may enter the lower respiratory airway via nasogastric and nasoduodenal tubes under mechanical ventilation. We confirmed that the drug-susceptibility profiles were the same in *P. aeruginosa* isolated from the paranasal cavity before surgery and from the lower respiratory tract after surgery. This mode of infection is known as VAT, as recently proposed by Craven et al (12). VAT is characterized as localized disease with clinical signs
(fever, leukocytosis, and purulent sputum), microbiologic information, and the absence of new infiltrates on chest radiograph, and VAT may progress to ventilator-associated pneumonia (VAP) in selected patients. Earlier administration of inhaled tobramycin, as suggested by Gram staining findings, followed by injection of tobramycin into the paranasal cavity were considered to be effective for the prevention of VAP and acquiring a good clinical outcome. Taken together, the information acquired from sequential Gram staining of specimens from the respiratory tract during the perioperative period was important for the prevention and early detection of VAT, as well as for selection of antibiotics to use in the management of infection after transplant surgery.

In conclusion, strict monitoring of clinical specimens from the respiratory tract by Gram staining is effective in preventing lower respiratory infection during the acute phase following lung transplant surgery in CF cases.

References


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