Early Bacterial Infections in Lung Transplant Recipients*

Engelbert Deusch, M.D.; Adelheid End, M.D.; Michael Grimm, M.D.; Wolfgang Graninger, M.D.; Walter Klepetko, M.D., F.C.C.P.; and Ernst Wolner, M.D.

Early bacterial pulmonary infections within 2 weeks after lung transplantation were studied in 29 patients undergoing surgery between December 1989 and May 1992. Suspected pulmonary infections occurred in 11 patients (38 percent). The most common bacterial organisms isolated were Klebsiella pneumoniae (45 percent; 5/11), Pseudomonas aeruginosa (36 percent; 4/11), Escherichia coli (37 percent; 3/11), Staphylococcus aureus (18 percent; 2/11), and Enterobacter cloacae (18 percent; 2/11). The mortality due to infection was 3 percent (1/29) in the early postoperative period. None of the following variables was found to be of prognostic significance: positive donor cultures, ischemic time of the graft, use of cardiopulmonary bypass, number of courses of methylprednisolone for acute rejection, duration of postoperative intubation, and type of surgical procedure. The presence of infection in the early postoperative period did not influence long-term survival. In the absence of prognostic parameters, prompt adjustment of antibiotic therapy to the results of antibiograms remains the most important therapeutic step in the management of infections in the early postoperative period after lung transplantation.

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ATG = antithymocyte globulin; FiO₂ = fraction of oxygen in the inspired gas; HPLC = high performance liquid chromatography; LTx = lung transplantation; MU = mega unit; OFF = oropharyngeal flora

Lung transplantation has become an acceptable treatment in end-stage lung disease. The diagnosis and treatment of infection and rejection in immunocompromised patients are challenging problems for physicians and surgeons. Infection is one of the most common causes of death in the postoperative period. Whereas fungal, protozoal, and viral infections occur later, bacterial infections with pneumonia as the main manifestation have a peak incidence in the first 2 postoperative weeks.

In a retrospective study, we analyzed the incidence and nature of bacterial pulmonary infections in lung transplant recipients within 2 weeks after operation in order to find putative prognostic factors for bacterial infection in this period.

**Materials and Methods**

**Patients and Surgical Procedure**

Between December 1989 and May 1992, there were 29 patients who underwent lung transplantation (LTX) (17 double; 12 single) at the Second Department of Surgery, University of Vienna. There were 16 men and 13 women with a mean age of 44 years (range, 22 to 67 years). Indications for surgery were idiopathic pulmonary fibrosis (n = 12), emphysema (n = 8), bronchiectasis (n = 2), cystic fibrosis (n = 2), primary pulmonary hypertension (n = 2), secondary pulmonary hypertension (n = 2), and Eisenmenger's syndrome with atrial septal defect (n = 1).

**Donor Selection.** Donors were selected according to ABO blood-group compatibility and were matched with the recipient for size, body weight, and chest circumference. For acceptance of the donor, a clear chest roentgenogram (for single lung transplantation, only on the transplanted side), a PaO₂ greater than 120 mm Hg at ventilation with a fractional concentration of oxygen in the inspired gas (FiO₂) of 30 to 45 percent, and a positive end-expiratory pressure (PEEP) of 5 cm H₂O were required. Fiberoptic bronchoscopy was performed to exclude aspiration or severe bronchitis. Moderate bronchitis was not a criterion for exclusion from transplantation. Lung preservation and explantation were performed as described elsewhere. The donors comprised 21 male and 8 female subjects with a mean age of 27 ± 10 years (SD) (range, 10 to 53 years). The causes of death were cerebral trauma (n = 18), bleeding from cerebral aneurysms (n = 7), cerebral thrombosis (n = 2), and gilblastoma (n = 1). The mean ischemic time was 303 min (range, 130 to 480 min).

**Surgical Procedure.** Surgery in the recipient was performed via a posterolateral thoracotomy for single lung transplantation and via an anterior bilateral transternal thoracotomy for sequential double lung transplantation. The bronchial anastomoses were performed either in telescope technique or in end-to-end fashion. In the period of study, no bronchial anastomotic problems such as dehiscence or stenosis occurred.

**Immunosuppression**

Induction of immunosuppression was started during surgery with 1,000 mg of methylprednisolone, followed by 3 doses of 125 mg every 8 h after surgery. Azathioprine was administered after surgery at a dosage of 2 mg/kg/day and was consecutively adjusted to the leukocyte count (WBC count > 4.5 x 10⁹/L). Depending on renal function, cyclosporin A was started intravenously at 54 to 48 h after surgery to achieve a whole blood level of about 300 ng/ml as measured by high-performance liquid chromatography (HPLC) (Biorad). Antithymocyte globulin (ATG) was given at a dosage of 10 mg/kg/day for the first 3 postoperative days. Intravenous therapy with methylprednisolone was followed by oral administration of corticosteroids at a dosage of 1 mg/kg/day, which was consecutively reduced to 0.5 mg/kg/day in the first 2 postoperative weeks.

**Antibiotic Regimen**

Before surgery, antibiotic prophylaxis was administered as follows: (1) a combination of penicillin G, 10 megaunits (MU) three times daily, with oxacillin 2 g, three times daily (n = 13); (2) cefuroxime, 3 g twice daily (n = 4); or (3) a combination of amoxicillin and clavulanate, 2.2 g three times daily (n = 4). Two patients with

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*From the Second Department of Surgery and the Division of Chemotherapy, Department of Internal Medicine, University of Vienna, Austria. Manuscript received November 25, 1992; revision accepted April 19, 1993. Reprint requests: Dr. End, 2nd Department of Surgery, University of Vienna, Spitalgasse 23, A-1090 Vienna, Austria.
cystic fibrosis primarily received broad-spectrum antibiotics such as a combination of imipenem and cilastatin, aztreonam, or clindamycin. In cases of allergy to penicillin, clindamycin was administered (n = 3). Different antibiotic regimens were applied in three cases. The postoperative antibiotic regimen was adjusted according to the antibiogram of the donor's and recipient's bronchial cultures. Prophylactic primary antibiotic therapy was continued for up to 6 days after surgery. Nystatin, 1.2 MU three times daily, was administered for oral myotic decontamination in all patients for at least 2 weeks after surgery. For oral hygiene, hexedine was used in the intensive care unit. After extubation, prophylaxis against *Pneumocystis carinii* infection was started with a combination of trimethoprim (160 mg) and sulfamethoxazole (800 mg) twice daily. Acyclovir in a dosage of 300 mg twice daily was added for 2 months to prevent herpes infection.

**Bacteriologic Monitoring**

During the operation, swabs for bacterial cultures were taken from the donor's bronchus and the recipient's bronchus. As transport medium, a commercially available system was used (Port-A-Cul Universal, Becton-Dickinson). When the operation was finished and the double-lumen tube was replaced by a single tracheal tube, fiberoptic bronchoscopy was performed by the surgeon to check the anastomoses and to perform bronchoalveolar lavage (BAL) with saline solution for bacterial and fungal cultures. Routinely, bronchoscopy with lavage was performed just before extubation in the intensive care unit. Depending on the clinical course, further bronchoscopy procedures were performed if necessary. During postoperative intensive care, bacterial samples of venous and arterial blood, urine, tracheal secretions, and swabs of the mouth and throat were taken routinely for culture every 3 days. Bacterial cultures of removed central venous or arterial lines were performed.

**Oropharyngeal flora (OPF)** comprised the following organisms: *Neisseria flava*, *Haemophilus haemolyticus*, *a*-hemolytic streptococci (*viridans streptococci*; "green strep"), Micrococcus, and diphtheroids (eg, * Corynebacterium sp*). *Haemophilus influenzae* is also found as part of the normal flora of the upper respiratory tract. Because *H influenzae* may cause severe infections in chronic respiratory ailments, we did not include it as part of OPF.

Although previously not considered to be significant causes of infection, coagulase-negative staphylococci are now presumably associated with an increasing number of infections, which are caused by *Staphylococcus epidermidis* in 70 to 80 percent of the cases. In the report, coagulase-negative staphylococci are referred to as their own entity, with their clinical significance in lung transplants not yet being known.

**Culture and Histologic Techniques**

Samples from BAL were stained with methylene blue, Giemsa stain, Gram's stain, and Ziehl-Neelsen stain for acid-fast organisms. Cultures for aerobic and anaerobic bacteria and fungi were taken. The diagnosis of colonization was made if more than 1,000 (less than 10<sup>9</sup>) colony-forming units per milliliter were found (see subsequent definition of infection). Transbronchial biopsies were performed only occasionally in the first 2 weeks after transplantation. Tissues were fixed in 7.5 percent buffered formaldehyde solution (Formalin), embedded in paraffin, and sectioned serially at 4 μm. Sections were stained with hematoxylin-eosin, Giemsa stain, periodic acid-Schiff (PAS), elastic van Gieson's stain, Grocott or Grocott-Gomori methenamine-silver stain, Gram's stain, and acid-fast stains. Rejection was graded according to the nomenclature of the Lung Rejection Study Group. In the group of 29 patients, early pulmonary infections occurred in 11 recipients (38 percent). Rejection episodes were suspected in 18 recipients (62 percent). Coincident allograft rejection and early pulmonary infection were suspected in 6 recipients (21 percent). Rejection episodes without coincident infection occurred in 12 recipients (41 percent). No early pulmonary infection or rejection episode was observed in 6 cases (21 percent). In patients with pulmonary infection, Gram-negative organisms were predominant (Table 1). In 4 (36 percent) out of 11 patients with infection, the same organisms were cultured from the donor bronchus and in postoperative BAL fluid from the recipient: *Serratia marcescens/S aureus, P aerugi-
nosa, and S aureus. In one patient who was free of infection, the same pathogen (E cloacae) could be cultured in the donor bronchus and BAL fluid.

Six patients underwent transbronchial biopsy within 14 days after surgery in order to differentiate between infection and rejection or to control the efficacy of antirejection therapy. All biopsies were classified as AO-A1; one biopsy demonstrated chronic bronchitis.

The two patients with cystic fibrosis had both P aeruginosa in their bronchial system at the time of transplantation. One of them developed pulmonary infection in the early postoperative period despite antibiotic prophylaxis with imipenem. Oropharyngeal flora was isolated in 6 (21 percent) out of 29 donor bronchial cultures. Fungal infections represented a minor problem in the early postoperative period. Five patients demonstrated fungal growth in BAL; two of them had simultaneous growth of bacteria in BAL and showed signs of infection. Three patients with fungal-positive BAL had no signs of infection.

**Prognostic Variables**

None of the following variables was found to be of statistical significance for the early bacterial infection rate: length of donor intubation, sex of recipient, diagnosis, surgical procedure (single vs double LTx), antibiotic prophylaxis (penicillin G-oxacillin combination vs cefuroxime or amoxicillin-clavulanate combination), ganciclovir prophylaxis, donor culture (sterile vs S aureus), use of cardiopulmonary bypass, number of methylprednisolone courses, and age of recipient (≤45 years vs >45 years). The group with infection did not differ from the group without infection in regard to allograft ischemic time and the duration of postoperative intubation (Table 2). Concerning antibiotic prophylaxis, cefuroxime and the amoxicillin-clavulanic acid combination tended to be superior to penicillin G combined with oxacillin alone, but the difference was not statistically significant.

**Mortality by Infection**

The mortality due to bacterial colonization which was associated with pulmonary infiltrates was 3 percent (1/29) in the early postoperative period. A 57-year-old woman died 8 days after single LTx. At autopsy lobar pneumonia caused by K pneumoniae was found, with generalized signs of sepsis.

**Survival**

The overall survival rate was 89 percent (26/29) and 76 percent (22/29) at 1 and 6 months, respectively (Kaplan-Meier estimate). Patients without pulmonary infection had a survival rate of 83 percent (15/18) at 1 to 6 months; patients with infection had a survival rate of 93 percent (10/11) and 73 percent (8/11) at 1 and 6 months, respectively. The difference is statisti-
cally not significant \((p > 0.05); \) generalized Wilcoxon-Breslow test).

Death from bacterial pulmonary infection beyond the study interval of 2 weeks occurred in 2 patients: on day 40 (patient without early infection) and 3 months after transplantation (patient with early infection).

**DISCUSSION**

In the early postoperative period after lung transplantation, infections of bacterial origin represent the most common cause of morbidity. Factors favoring infections comprise immunosuppressive therapy with corticosteroids, azathioprine, and cyclosporin A due to different mechanisms. Local factors such as impaired mucociliary clearance in the transplanted lung, \(10^7\) severed lymphatics, \(10^8\) altered bronchial circulation, and transfer of infectious agents from the donor lung contribute to postoperative infections. Transfer of bacteria from a donor to a recipient causing clinical pneumonia in the latter was demonstrated in an experimental canine model. \(10^9\)

Heart-lung transplant recipients who suffered from infections within 2 weeks after transplantation had a significantly lower survival rate compared with those who were free of infection. The presence of OPF in the donor tracheal culture was associated with the onset of early infection and considered to be of prognostic significance. \(10^{10}\) Sufficient data are available in heart-lung transplant recipients, \(10^{11}\) whereas studies in a homogeneous population of lung transplant patients are missing. Although there is no difference in exposure of the lungs to environmental influences in lung and heart-lung transplants, the different approach for the surgical technique (tracheal vs bronchial anastomoses; mediastinal dissection), the use of cardiopulmonary bypass, and different immunosuppressive regimens at our institution might influence the pattern and rate of postoperative infection. Therefore, we performed a retrospective analysis of bacterial pulmonary infections in 29 lung transplant recipients, with special attention to putative prognostic risk factors for infection.

The most difficult point in the assessment of early postoperative infection in lung transplant recipients is the differential diagnosis between pulmonary infection and allograft rejection because of similar symptoms. Besides, infection and rejection often coexist. It is quite astonishing that in published reports, there are often clear figures for both conditions; however, in personal discussions, doubts and severe difficulties in differentiation are admitted. \(10^{12}\) From clinical practice, we know the biased judgments of clinical symptoms depending on the personal views of the transplant surgeon, the intensive-care specialists, or consulting physicians and chemotherapists. When no consensus is reached, the final treatment often results in antirejection therapy, as well as in broad-spectrum antibiotic therapy. To overcome this bias, an independent investigator tried to categorize clinical symptoms as rejection or infection and to find a consensus with all of the members of our transplant team; however, analysis and abstraction of the large quantity of data are not easy and do not match the polymorphic postoperative course of lung transplant recipients completely.

In our patients the suspected pulmonary infection rate was 38 percent, which is comparable to the literature. \(10^{13}\) For the occurrence of infection, no prognostic risk factor could be determined. Variables such as ischemic time, the use of cardiopulmonary bypass, the number of pulse-prednisolone courses, the duration of intubation, sex, and the surgical procedure (single vs double LTx) did not differ significantly in the group with \((n = 11)\) and the group without infection \((n = 18)\). There was also no statistical difference in survival; however, the group with infection seemed to have a poorer prognosis in the first 3 months, and afterwards the rate was reversed. The mortality was 3 percent due to death from \(K\ pneumoniae\), with consecutive sepsis on the 8th postoperative day. Retrospectively, this patient was considered a poor candidate for transplantation because of deconditioned physical status and high age.

There is no correlation between the species of bacteria isolated from donor bronchial cultures and the isolates from postoperative bronchoalveolar lavage fluid in patients with pulmonary infection. In 4 out of 12 patients with infection, the same pathogens were cultured: in 3 of them at 1 to 3 days after surgery and in the 4th \(S\ aureus\) was found on day 11 together with Klebsiella, so bacterial pneumonia might be caused by the donor-transmitted \(S\ aureus\) or the newly gathered Klebsiella (or both). On the other hand, fungal infections play a minor role in the immediate postoperative period. In two patients, \(Candida\) sp might have contributed to pneumonia also caused by bacteria. No invasive candidiasis was observed in our patients.

In contrast to other authors, we are not so concerned about the presence of \(S\ aureus\) in the donor bronchus, \(10^{14}\) because it is often found in patients on long-term respirator therapy. \(Staphylococcus aureus\) was cultured in 41 percent (12/29) of donor bronchial cultures, and 6 of the patients developed an infection, but 4 of them also had other isolates in bronchoalveolar lavage fluid contributing to infection. In summary, morbidity due to \(S\ aureus\) alone was low in our patients, which may have been the result of sufficient antibiotic prophylaxis.

The presence of OPF in the donor bronchus is considered by some authors to be associated with the onset of early infection as a consequence of silent
aspiration. However, we did not see any correlation between OPF in the donor bronchus and the infection rate. There were 83 percent of the patients with positive OPF donor cultures (5/6) who remained free of infection. Only one patient with preexisting colonization of his bronchial system developed an infection with mixed bacterial BAL cultures.

When starting with the lung transplantation program at our institution, recipients received the penicillin G-oxacillin combination, except for the patients with cystic fibrosis, who received additional aminoglycosides or an imipenem-cilastin combination, aztreonam, or clindamycin. When we gained more experience, antibiotics with Gram-negative coverage, such as cefuroxime or the amoxicillin-clavulanate combination, were used; in our opinion, they tended to be superior to the penicillin G-oxacillin combination.

The lack of significant risk factors in our group may be due to the small amount of data or the intentional renunciation of sophisticated statistical methods; however, this lack confirms our belief that a successful outcome after lung transplantation is a function of a multitude of factors which cannot easily be grasped in a statistical analysis. With attention to these factors, the high morbidity due to pulmonary infections after lung transplantation will be lowered by an aggressive diagnostic approach with immediate adjustment of antibiotic treatment to current cultural findings.

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