Outcome of patients with cystic fibrosis admitted to the intensive care unit: Is invasive mechanical ventilation a risk factor for death in patients waiting lung transplantation?

Ori Efrati, MD, Irena Bylin, MD, Eran Segal, MD, Daphna Vilozni, PhD, Dalit Modan-Moses, MD, Amir Vardi, MD, Amir Szeinberg, MD, and Gideon Paret, MD

OBJECTIVE: The admission of patients with cystic fibrosis (CF) to the intensive care unit (ICU) is controversial. Our aim was to study the long-term outcome of patients with CF who were admitted to the ICU and the effect of ventilation modality.

METHODS: The medical records of 104 admissions (1996-2006) of 48 patients with CF (age 18 ± 9 years) were reviewed. Seventeen patients were admitted with reversible conditions (group 1). Thirty-one patients were admitted for acute on chronic respiratory failure (group 2).

RESULTS: In group 1, 16 of 17 patients survived up to 10 years from ICU admission. Conversely, in group 2, 23 of 31 patients (74%) died of respiratory failure. In group 2, 17 of 18 patients who were mechanically ventilated died within 90 days from admission, and 7 of 10 patients treated for prolonged periods with bi-level positive airway pressure are still alive up to 10 years after admission and transplantation.

CONCLUSION: Patients requiring mechanical ventilation may have a poor prognosis. The outcome of treatment with bi-level positive airway pressure is good, even in patients who had many episodes of acute respiratory failure. (Heart Lung 2010;39:153–159.)

Cystic fibrosis (CF) is an incurable multisystem genetic disorder with a median predicted survival of approximately 35 years despite new therapies, including lung transplantation (LTx). Lung disease is the primary cause of morbidity and mortality in CF and is characterized by progressive episodes of airway infection and inflammation, which eventually lead to respiratory failure. Respiratory failure and end-stage lung disease are the cause of death in more than 80% of patients with CF. After a study by Davis and di Sant’Agnese showing a poor outcome for patients with CF requiring mechanical ventilation (MV), many centers have refrained from intubating patients with CF with end-stage lung disease. However, more recent studies have demonstrated an improvement in survival rates and favorable prognosis in patients with CF requiring invasive MV because of acute respiratory failure. Moreover, new treatment modalities have emerged in the intensive care unit (ICU), particularly the use of bi-level positive airway pressure (BiPAP), a noninvasive mode of ventilation administered through a tight-fitting mask. The device cycles spontaneously between the pre-set levels of inspiratory and expiratory positive airway pressures. This has enabled successful discharge from the ICU, overcoming acute on chronic respiratory failure without the need for intubation. BiPAP can also be used as a long-term therapy, as a bridge for LTx, and may prevent post-transplant lung infection and acute rejection and improve long-term survival after LTx.
Because the survival of patients with CF is continuously increasing, new indications for admission to the ICU arise: percutaneous endoscopic gastrostomy (PEG) insertions, drug desensitization, instruction in the use of noninvasive positive pressure ventilation (NIPPV) techniques, and life-threatening but reversible complications, such as pneumothorax or hemoptysis. Nevertheless, whether patients with CF should be admitted to the ICU is still debatable, in particular patients requiring invasive MV.

The aims of this study were to a) assess the short- and long-term outcomes of all patients with CF admitted to the ICU in our center during a 10-year period, b) identify risk factors associated with a poor prognosis, and c) study the outcomes of patients with CF with acute respiratory failure treated with invasive MV.

PATIENTS AND METHODS

Patient recruitment

We reviewed the records of all 155 patients with CF followed in the CF center of the Pulmonary Unit at the Sheba Medical Center, Tel Hashomer, Israel, between 1996 and 2006. All 48 patients with CF admitted to the ICUs in our center between 1996 and 2006 (pediatric and adult) were included in the current analysis. When a patient had multiple ICU admissions, the first admission was considered as the index hospitalization.

The study was approved by the medical ethics committee of our hospital. The diagnosis of CF was based on the sweat chloride test or identification of CF transmembrane conductance regulator mutations, and at least 1 typical clinical manifestation. Acute respiratory failure was defined as respiratory deterioration (hypoxemia < 60 mm Hg, respiratory acidosis with arterial pH of < 7.25 to 7.30, neurologic signs of hypercarbia, and evidence of respiratory muscle fatigue) necessitating NIPPV use or intubation with MV.

Measures

The clinical characteristics of the patients were obtained by reviewing their medical charts. Patients admitted to the ICU after LTx were excluded. The data included cause of admission, outcome (death or survival time from hospital discharge), length of stay in the ICU, mode of ventilation in the ICU, and spirometric data (best forced vital capacity [FVC] and forced expiratory volume at 1 second [FEV1]) at the time of admission. Age, sex, CF transmembrane conductance regulator mutation, arterial blood gases, presence of pancreatic insufficiency, body mass index (BMI), presence of associated disease such as CF-related diabetes, portal hypertension, liver disease, and bacterial colonization, in particular Pseudomonas aeruginosa or Staphylococcus aureus, were recorded. The study end point was mortality during the ICU stay and long-term survival after ICU discharge, with a follow-up of up to 10 years.

Management

All patients, except for those who had hemoptysis or pneumothorax, underwent physiotherapy at least twice per day. Every patient was treated with intravenous antibiotics, chosen according to the sensitivity of the bacteria isolated from the sputum.

Ten patients, who were listed for transplantation, were treated with BiPAP before the initial ICU admission. These patients continued BiPAP therapy in the ICU during pulmonary exacerbation, with adjustment of BiPAP settings as needed.

In addition, when pulmonary exacerbation was the reason for the ICU admission, the first modality of ventilatory support was the application of NIPPV (BiPAP device: S/T Respironics, Monroeville, PA) through a full face mask. The initial setting of the inspiratory peak pressure was 6 cm H2O, and the expiratory positive airway pressure was set at 2 to 3 cm H2O on the spontaneous mode of ventilation. Pressures were increased in increments of 2 cm H2O and adjusted to optimize the patients’ comfort. The maximal inspiratory positive pressure reached 20 to 24 cm H2O, and the expiratory positive pressure reached 10 to 12 cm H2O. When NIPPV failed to stabilize the patient (depressed level of consciousness, inability to coordinate with NIPPV, or severe acidosis and hypoxemia), invasive MV via endotracheal tube was initiated. Hypoxemia and hypercarbia per se were not an absolute indication for intubation.

Patients were referred for LTx according to the consensus conference statement criteria: progressive pulmonary function impairment manifested by FEV1 < 30% and severe hypoxemia and hypercarbia, increasing functional impairment, or major life-threatening complications such as uncontrolled hemoptysis. Although psychologic and social dysfunction are considered a relative contraindication to LTx, none of our patients were denied transplantation on the basis of these criteria. Unlike the situation in other countries such as the United Kingdom, in Israel once a patient was mechanically ventilated she/he was promoted to the head of the national transplant list. Thus, of all the patients included in the study, only 1 patient was not offered LTx, because she had chronic hepatitis B, which at the time was an absolute contraindication for transplantation.
Data analysis

For the purpose of analysis, the patients were divided into 2 groups according to the cause of hospitalization in the ICU. Group 1 included 17 patients with reversible complications necessitating ICU admission: PEG insertion, instruction in the use of BiPAP, pneumothorax, and hemoptysis. Group 2 comprised 31 patients admitted because of acute on chronic respiratory failure, as defined above (respiratory acidosis with arterial pH of < 7.25-7.30, neurologic signs of hypercarbia, and evidence of respiratory muscle fatigue).

To assess the short- and long-term outcomes, we analyzed survival after discharge from ICUs using the Kaplan–Meier method, comparing the 2 groups by the log-rank test. To identify risk factors associated with a poor prognosis, we compared group 1 with group 2, and BiPAP users versus invasively ventilated patients within group 2. Categoric variables were compared using the Fisher’s exact test, and quantitative variables were compared using the Student t test.

Analyses were performed using the Statistical Package for the Social Sciences software 11.0 for Windows (SPSS Inc, Chicago, IL). Quantitative variables are expressed as mean ± standard deviation. Results were considered significant if the 2-sided P value was less than .05.

RESULTS

From 1996 to 2006, there were 104 admissions of 48 patients with CF (aged 18 ± 9 years; range 5-43 years) to the ICU. Most patients (n = 36, 75%) had their first ICU admission before 2001. Twenty-four of the 48 patients (50%) survived the ICU stay, were discharged from hospital, and are still alive 3 to 10 years after the initial ICU admission.

*P. aeruginosa* was isolated in 41 of 48 patients (85.4%). All patients had pancreatic insufficiency. The anthropometric data, basic lung function, clinical data, and survival of both groups of patients are presented in Table I.

**Mean age**

Mean age at the first ICU admission was not significantly different between the 2 groups. Group 2 included an infant aged 6 months at the time of admission and 2 patients aged 6 years. Otherwise, both groups included young adolescents (aged 10-16 years).

**Nutritional status**

Nutritional status, as reflected by BMI at admission to ICU, was severely low in both groups (BMI of 16.6 ± 2.6; z score −2.36 ± 0.6 vs BMI of 16.9 ± 2.4; z score −2.2 ± 0.8 groups 1 and 2, respectively).

**Lung function (presented by spirometry)**

Group 1 patients had significantly better FVC and FEV1 values than group 2 patients, who manifested severe obstructive lung disease (P < .009 for FVC and P < .0032 for FEV1, respectively).

*Staphylococcus aureus*. *S. aureus* was isolated in 16% (5/31) of group 2, compared with only 1 patient in group 1 (P < .05).

**Intensive care unit stay**

Length of stay in the ICU was significantly shorter in group 1 (4.6 ± 3.6 days vs 10 ± 6 days, P < .0005). A single patient (3%) from group 1 died during the ICU hospitalization as a result of electrolyte imbalance and convulsions.

**Mortality**

Mortality was significantly higher in group 2 compared with group 1 (P < .005). Twenty-three of 31 patients in group 2 (74%) died of respiratory failure, 16 (51.6%) of them during the initial ICU stay, compared with 1 patient (3%) in group 1, who died during the ICU hospitalization as a result of electrolyte imbalance and convulsions (Fig 1).

**Associated disease**

The presence of associated disease did not differ between the groups. Twelve patients in group 1 and 14 patients in group 2 had CF-related diabetes. Seventeen patients (35%) in group 1, compared with 9 patients (18.7%) in group 2, had liver disease and cirrhosis.

**Genetics**

All patients carried at least 1 severe mutation; 62.5% carried W1282X, with no difference between the 2 groups, and 17% of the patients carried at least 1 delta F508 allele.

**Arterial blood gases**

Arterial blood gases measured on ICU admission, in particular CO2 tension, did not differ significantly between the 2 groups and did not influence the outcome.
Mechanical ventilation

Eighteen of group 2 patients required invasive MV because of acute on chronic respiratory failure (Table I). Seventeen of these patients (94.4%) died during the study period, 14 of them within 90 days of the ICU admission (Fig 2). Only 1 patient, a 6-month-old infant, was extubated successfully and is still alive 6 years after his first admission, albeit with moderate-to-severe lung disease, as reflected by his reduced FEV1. Six patients were on the list for LTx but died before a donor could be found. Another 6 of the mechanically ventilated patients underwent LTx during the ICU admission. All of them died, 3 of them during the acute phase (1-2 months after LTx) (Fig 2).

Lung transplantation (group 2)

Ten patients underwent LTx after using BiPAP for prolonged periods (Table I). The mean duration of BiPAP use was 8 months (range 3-16 months). Seven patients (70%) are still alive 2 to 8 years after LTx. Only 3 patients in this subgroup died during the study period, as a result of bronchiolitis obliterans (Fig 3).

Three patients with end-stage lung disease were admitted to the ICU and underwent LTx within 3 days of admission without any ventilation. They all died within 3 years after the procedure (1 patient during the first week after LTx).

DISCUSSION

The present study evaluated the long-term outcome of 48 patients with CF admitted to the ICU and compared the outcome of patients with CF requiring invasive MV with those treated with NIPPV, during a 10-year period. All patients were followed...
up and treated at the same accredited CF center. Our results show a high mortality rate (94.4%) among patients admitted to the ICU and treated with MV for acute on chronic respiratory failure. In contrast, the survival rate among patients using BiPAP for prolonged periods of time before transplantation was high.

It could be argued that invasive ventilatory support may be appropriate for patients with CF when LTx can be achieved within a short time, such as in living-relative LTx. However, in our 6 patients who were mechanically ventilated as a bridge to transplantation, the prognosis was poor, and none of them survived during the 10-year study period.

Factors that may have contributed to the decreased survival of mechanically ventilated patients included copious, viscous secretions in the airways; difficulty in clearance of secretions; ciliary dismotility; large bronchiectases; diffuse lung parenchyma destruction with stiff lung; and reduced compliance. The only patient who survived MV and is still alive 6 years after ICU discharge was a 6-month old infant who had acute respiratory failure, similar to the findings of Berlinski et al, who showed a better outcome in infants and young patients with CF who required invasive ventilation. This finding may be attributed to the high pulmonary reserve and growth of lung parenchyma at this age.

Thirty years ago, Davis and di Sant’Agnese demonstrated a high mortality rate in patients with CF who underwent MV. Moreover, Elizur et al showed increased early post-transplant morbidity and mortality in patients with CF ventilated before transplantation. They found that patients ventilated before LTx showed a significant increase in early graft failure and dysfunction. Our results are consistent with those of Berlinski et al and Ellaffi et al, who demonstrated that the majority of patients intubated because of pulmonary exacerbation died. Even Sood et al showed a less favorable outcome in patients with acute respiratory failure who were ventilated, with nearly half dying in the ICU, and the majority of survivors subsequently undergoing LTx. Unlike other investigators, we followed our patients for up to 10 years after LTx. Unfortunately, all our patients who were mechanically ventilated and subsequently underwent LTx died within 1 month to 9 years after the procedure, mostly in the immediate post-LTx period (1-9 months).

In many CF centers, the admission to the ICU of critically ill patients with end-stage lung disease is not considered, and even patients listed for LTx are often removed from waiting lists because of their deterioration and need for MV. The results of a UK study showed a low rate of survival (16%) in patients who required endotracheal intubation after a follow-up of 6 months. Similarly, our results showed a poor outcome in patients who were intubated and did not undergo LTx during their ICU stay. Severely restricted organ availability and the disappointing outcome of ventilated patients who undergo LTx may reduce the enthusiasm to operate...
on this group of patients. Ten of our patients under-
went LTx after prolonged BiPAP use. It would seem
that the outcome in this group is good, even in pa-
tients who had many episodes of acute respiratory
failure, exacerbations, and multiple admissions to the ICU before LTx (70% survival 3-10 years
after the procedure). This ventilation modality facili-
tates coughing and clearance of secretions, and
permits better physiotherapy with special tech-
niques.6,7,13,17,18 We previously demonstrated that
long-term BiPAP use can improve survival, stabilize
and improve physiologic parameters, such as arterial
blood gases (in particular, reduction in PaCO2), in-
crease BMI, and improve subjective symptoms such
as sleep patterns and daily activity in patients with
end-stage lung disease awaiting LTx.8,9 We hypothe-
size that improvement in nutritional status, acid-
basis balance, and respiratory muscle strength before
LTx in our BiPAP users may prevent post-LTx infec-
tion and acute rejection rates, thus reducing the
risk of development of bronchiolitis obliterans or
chronic rejection.9 We therefore recommend that pa-
tients with CF with end-stage lung disease and se-
verely low FEV1 (~30% of predicted values) should
be instructed in the use of BiPAP.6,11,18,19
The growing number of adults with CF (≈ 60%) in
our center and the increasing median survival age of
patients with CF increase the number of pulmonary
and extrapulmonary reversible complications that
can be treated successfully in the ICU setting. The re-
cent introduction of new procedures and treatment
modalities, such as PEG insertions and NIPPV edu-
cation and instruction, has resulted in better man-
agement of life-threatening conditions, such as
massive hemoptysis, pneumothorax and pleurode-
sis, varices ligation, and severe liver disease. Indeed,
only 1 patient (3%) in group 1 died after ICU ad-
mission and treatment of patients with CF with end-stage respiratory failure,16 and in contrast with those of Sood et
al,7 none of our patients who were intubated and me-
chanically ventilated survived to LTx, except for 3 pa-
tients who underwent living-related bilobar transplanta-
tion. This is probably because of the limited
number of organs available and the different ways in which the National Center for Transplanta-
tion prioritizes patients for transplantation. More-
over, the outcome of the 3 patients who underwent
living-related bilobar transplantation was also poor.
Our analysis revealed that of all the variables
studied, MV was the major and immediate risk fac-
tor for death in patients with CF with end-stage
lung disease. The presence of S. aureus in the lower
airways was another risk factor for death in patients
who were admitted to the ICU with lung failure
(16%).

LTx is still associated with high mortality, with
a 5-year survival rate of approximately 45% for pa-
tients with CF and other patients.21 Liou et al,1 after
performing survival modeling using interactions of
multiple covariates, recently analyzed the effect of
LTx on the survival of children with CF. They esti-

mated that improved survival was achieved in
only 5 of 514 patients on the waiting list for LTx.
Moreover, they concluded that LTx in itself does
not improve survival in children with CF, or it would
be expected to prolong life in those patients whose
predicted median survival period is less than 3
years without LTx.

The lack of evidence that LTx improves survival1
and the high mortality rate in our patients who re-
ceived invasive MV for respiratory failure suggest
that endotracheal intubation and MV of patients
with CF with acute on chronic respiratory failure
should be discouraged. This makes the decision to
admit these patients to the ICU a difficult one.
Whenever possible, both patients and their families
should be informed about the poor prognosis.

STUDY LIMITATIONS
Several limitations to our study should be consid-
ered. First, this was a retrospective study. However,
such studies cannot be designed prospectively. In
addition, we did not study the different modes of
ventilation in a double-blind manner. Some of our
patients who were listed for LTx did not have the op-
portunity to use BiPAP because at the time they were
admitted to the ICU (7-10 years ago) this mode of
ventilation was not frequently used. In contrast,
over the past few years, BiPAP was offered to all pa-
tients because of our favorable recent experience
with this mode.

CONCLUSIONS
Our study indicates a poor prognosis in patients
requiring MV, either for acute respiratory failure or
during the period awaiting LTx. When possible, end-stage lung disease can be treated successfully
with BiPAP, which can serve as a bridge while await-
ing LTx. Reversible pulmonary and extrapulmonary
complications can be managed appropriately in the ICU setting.

REFERENCES