Randomized controlled trials have shown that noninvasive ventilation (NIV) reduces the need for endotracheal intubation and invasive mechanical ventilation and reduces complication rates and mortality in selected groups of patients. The best evidence of this was obtained from patients with exacerbation of chronic obstructive pulmonary disease (COPD) and severe cardiogenic pulmonary edema (CPE). Application of the results of randomized controlled trials of NIV to patients admitted to intensive care units (ICUs) might therefore result in an improved survival rate. Cohort studies have also suggested that implementation of NIV results in a decrease in the rate of nosocomial pneumonia and infections.

However, evidence from randomized trials may not translate into clinical practice for several reasons. The implementation of NIV out of the context of a clinical trial may necessitate extensive education and training of the medical and nonmedical staff. The first hours of NIV are associated with an increased workload for health care personnel that requires a specific management protocol, including monitoring mask ventilation and monitoring patients because they do not receive sedation. Managing patients receiving NIV differs from managing patients receiving mechanical ventilation in particular because they less frequently receive arterial lines or central venous access, both allowing close monitoring. All of these factors may limit the application of NIV by clinicians and

Context Randomized controlled trials have shown that the use of noninvasive ventilation (NIV) reduces the need for endotracheal intubation and invasive mechanical ventilation and reduces complication rates and mortality in selected groups of patients. But whether these benefits translate to a clinical setting is unclear.

Objective To evaluate longitudinally the routine implementation of NIV and its effect on patients admitted to the intensive care unit (ICU) with acute exacerbation of chronic obstructive pulmonary disease (COPD) or severe cardiogenic pulmonary edema (CPE).


Setting A 26-bed medical intensive care unit (ICU) of a French university referral hospital.

Participants A cohort of 479 consecutive patients ventilated for acute exacerbation of COPD or CPE.

Main Outcome Measures The ICU mortality and incidence rates of ICU-acquired infections.

Results A significant increase in NIV use and a concomitant decrease in mortality and ICU-acquired infection rates were observed over the study years. With adjustment for relevant covariates and propensity scores, NIV was identified as an independent factor linked with a reduced risk of death in the cohort (odds ratio [OR], 0.37; 95% confidence interval [CI], 0.18-0.78), whereas a high severity score on admission (OR, 1.05; 95% CI, 1.01-1.10) and the occurrence of a nosocomial infection (OR, 3.08; 95% CI, 1.62-5.84) were independently associated with death. Rates of ICU-acquired pneumonia decreased from 20% in 1994 to 8% in 2001 (P = .04).

Conclusion Implementing routine use of NIV in critically ill patients with acute exacerbation of COPD or severe CPE was associated with improved survival and reduction of nosocomial infections.
may limit the extent to which the mortality benefit found in randomized trials is realized in practice.13,14

The objective of this study was to evaluate longitudinally the routine implementation of NIV and its effect on ICU survival of patients with exacerbation of COPD or acute CPE. We began the study in 1994 after completion of a randomized controlled trial evaluating the efficacy of NIV in patients with acute exacerbation of COPD.3

METHODS
Setting and Population
The study was conducted in the medical ICU of Henri Mondor University hospital in Créteil, a 26-bed ICU that receives patients from the community, from other departments or specialized ICUs in the hospital, or from other hospitals. The study period extended from January 1, 1994, through December 31, 2001, during which time 8,206 patients were admitted to the ICU.

We conducted a retrospective search of all eligible patients, including all consecutive patients admitted for acute exacerbation of COPD or severe CPE and in whom ventilatory support with either conventional mechanical ventilation (CMV) or NIV was initiated within the ICU as initial ventilatory support, excluding patients for whom NIV was used for postextubation respiratory distress or as a weaning modality. Because the hospital has a large coronary care unit, patients referred to the ICU with a diagnosis of CPE constitute a selected population among all CPE patients. They are preferentially transferred to the medical ICU in case of comorbidities (especially chronic bronchitis), old age, and hypercapnic respiratory failure. Patients with associated diagnoses, such as acute asthma or pulmonary embolism; patients after surgery or requiring surgery; patients with metastatic cancer or hematological malignancy with a poor short-term prognosis and/or with a do-not-resuscitate order on admission; and patients with acute lung injury were not included in the analysis. Similarly, patients presenting with coma or shock (contraindications to NIV use) were not kept in the analysis. We considered patients in shock if they had received epinephrine or norepinephrine within the first 48 hours of ICU admission. Coma was defined by a Glasgow Coma Scale score of less than 10 on admission. Inclusion and exclusion criteria for the study were developed a priori. We decided to combine the analysis for patients with COPD and CPE for the following reasons: these 2 populations constitute relatively homogeneous groups, in which the benefits of NIV have been demonstrated through randomized controlled trials. In both cases, the pathophysiology of the decompensation is characterized by acute ventilatory failure, increased work of breathing, and most often a progressive increase in arterial carbon dioxide. The effect of NIV on work of breathing, alveolar ventilation, and patients’ dyspnea are very similar in the 2 groups of patients. As mentioned above, many of the CPE patients included in this study had a mild degree of coexistent chronic respiratory abnormalities.

Noninvasive ventilation was applied intermittently, for daily periods of at least 6 hours. Pressure support with positive end-expiratory pressure was the mode of ventilation. The usual setting was 12 to 20 cm of water of pressure support and 0 to 5 cm of water of positive end-expiratory pressure.

Data from 50 patients receiving NIV from 1996 to 1998 and 50 patients treated with invasive mechanical ventilation from 1994 to 1998 have been presented in part in a previously published study.10

Data Collection
We prospectively collected the following information: age; admission and discharge dates from the ICU; primary diagnosis; severity scores on admission, Simplified Acute Physiology Score (SAPS) II17 and Logistic Organ Dysfunction (LOD) score18; treatments administered initially including antibiotics, bronchodilators, diuretics, and steroids; and outcome at ICU discharge. We also recorded the sites and dates of diagnosis of all nosocomial infections. According to previously defined criteria,19 we screened for pneumonia, urinary tract infection, primary bacteremia, central venous catheter-related infection that may have occurred at least 48 hours after ICU admission. Surveillance was performed prospectively by a physician (C.B.B.) who weekly reviewed all clinical and microbiological information.

Statistical Analysis
A sample size calculation indicated that 438 patients would be needed to detect a 10% absolute reduction in mortality among patients receiving NIV compared with CMV, at a significance level of 5% and a power of 80%.

Categorical variables were expressed as percentage and continuous variables as median and interquartile range (IQR). A P value of .05 or less in a 2-tailed test was considered statistically significant. Categorical variables were compared with use of the χ² test or Fisher exact test, and continuous variables with the t test. Nonparametric tests were used when the conditions for parametric tests were not fulfilled (ie, Mann-Whitney test for continuous variables). Confidence intervals (CIs) of proportions were calculated according to the Wilson method.19 Failures of NIV treatment were retained in the NIV group.

A time-trend analysis was performed using logistic regression analysis to determine changes over time in NIV use, nosocomial infection, and mortality rates.20 Changes over time of patients’ severity, medical treatment, and other outcome variables were also analyzed with logistic regression for categorical variables and with linear regression for continuous variables.

Variables found to be associated with death in the univariate analysis (P<.10) were entered into a stepwise logistic regression model to estimate adjusted odds ratios (ORs) and 95% CIs. Due to the collinearity of SAPS II and the LOD score and of ICU-acquired infections...
and ICU-acquired pneumonia, only SAPS II and ICU-acquired infections were entered into the multivariate model. Noninvasive ventilation, bronchodilators, and year were also entered in the model. Continuous variables were not dichotomized.

In addition to adjusting for significant covariates in multivariate analysis, residual confounding and selection effects were addressed using propensity scores.23,24 To develop the propensity score for NIV use, we first performed a stepwise logistic regression analysis of all factors that differed in the NIV and CMV groups, using a significance criterion of P<.10. These factors included age, SAPS II, LOD score, year of admission, diagnosis, and bronchodilator use. In the propensity regression analysis, we assigned mean levels of continuous covariates (LOD score) and modal levels of binary covariates (administration of antibiotics, bronchodilators, diuretics, steroids) to patients with missing data (n=30).

With NIV use as the dependent variable, we fitted a model predicting the propensity of NIV use. Using this model, patients were classified by quintile of increasing probability of receiving NIV. We then incorporated the propensity score as a covariate in a stepwise logistic regression model using mortality as the dependent variable.

The statistical analysis was performed using Epi-Info 6.0 (Centers for Disease Control and Prevention, Atlanta, Ga) and STATISTICA 4.5 (Statsoft Inc, Tulsa, Okla).

RESULTS

During the 8-year period of this study, 8206 patients were admitted to the ICU, of whom 521 received NIV, CMV, or both for acute exacerbation of COPD or severe CPE. Among these, 479 (92%) fulfilled our criteria for inclusion in the cohort (Figure 1). The number of patients included, their severity on admission, and the medical treatment provided during the 8-year study period are shown in Table 1. No change over these years occurred in severity level or medical treatment except for the use of NIV.

As shown in Figure 2, the utilization rate of NIV during the 8-year study period gradually and significantly increased among these 479 patients receiving ventilatory support in the unit (P<.001). Meanwhile, the crude ICU mortality rate of these patients significantly decreased from 21% in 1994 to 7% in 2001 (P=.04). A significant reduction was also found in the in-hospital mortality rates over the years, from 24% in 1994 to 11% in 2002 (P=.009). These results, however, do not

Table 1. Changes Over Time of Patients’ Severity, Medical Treatment, and Outcome During the Study Period

<table>
<thead>
<tr>
<th>Variable</th>
<th>1994 (n = 39)</th>
<th>1995 (n = 52)</th>
<th>1996 (n = 64)</th>
<th>1997 (n = 61)</th>
<th>1998 (n = 70)</th>
<th>1999 (n = 63)</th>
<th>2000 (n = 58)</th>
<th>2001 (n = 72)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbation of COPD</td>
<td>33 (85)</td>
<td>37 (71)</td>
<td>41 (61)</td>
<td>45 (74)</td>
<td>52 (74)</td>
<td>51 (81)</td>
<td>43 (74)</td>
<td>56 (78)</td>
<td>.49</td>
</tr>
<tr>
<td>Severe CPE</td>
<td>6 (15)</td>
<td>15 (29)</td>
<td>23 (36)</td>
<td>16 (26)</td>
<td>18 (26)</td>
<td>12 (19)</td>
<td>15 (26)</td>
<td>16 (22)</td>
<td></td>
</tr>
<tr>
<td>Diagnostic score, median (IQR), points*</td>
<td>35 (28-41)</td>
<td>40 (30-47)</td>
<td>36 (32-42)</td>
<td>38 (31-46)</td>
<td>40 (33-47)</td>
<td>37 (31-47)</td>
<td>36 (30-41)</td>
<td>36 (30-40)</td>
<td>.21</td>
</tr>
<tr>
<td>SAPS II</td>
<td>3 (1-5)</td>
<td>4 (3-6)</td>
<td>3 (1-5)</td>
<td>4 (2-6)</td>
<td>4 (2-6)</td>
<td>4 (2-6)</td>
<td>3 (2-5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.68</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>67 (64-76)</td>
<td>67 (64-73)</td>
<td>70 (62-77)</td>
<td>71 (65-77)</td>
<td>73 (67-77)</td>
<td>72 (61-80)</td>
<td>71 (66-76)</td>
<td>70 (62-75)</td>
<td>.62</td>
</tr>
<tr>
<td>Initial ICU medication, No./total (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>13/35 (37)</td>
<td>27/42 (64)</td>
<td>23/57 (40)</td>
<td>29/56 (52)</td>
<td>24/66 (36)</td>
<td>20/63 (32)</td>
<td>23/58 (40)</td>
<td>28/72 (39)</td>
<td>.08</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>12/35 (34)</td>
<td>9/42 (21)</td>
<td>21/57 (37)</td>
<td>22/56 (39)</td>
<td>23/66 (35)</td>
<td>28/63 (44)</td>
<td>23/58 (40)</td>
<td>28/72 (39)</td>
<td>.13</td>
</tr>
<tr>
<td>Diuretics</td>
<td>12/35 (34)</td>
<td>22/42 (52)</td>
<td>32/57 (56)</td>
<td>33/56 (59)</td>
<td>40/66 (60)</td>
<td>37/63 (59)</td>
<td>30/58 (52)</td>
<td>31/72 (43)</td>
<td>.97</td>
</tr>
<tr>
<td>Steroids</td>
<td>7/35 (20)</td>
<td>10/42 (24)</td>
<td>11/57 (19)</td>
<td>9/56 (16)</td>
<td>12/66 (18)</td>
<td>8/63 (13)</td>
<td>12/58 (21)</td>
<td>13/72 (18)</td>
<td>.55</td>
</tr>
<tr>
<td>ICU-acquired pneumonia, No. (%)</td>
<td>8 (20)</td>
<td>5 (10)</td>
<td>10 (16)</td>
<td>6 (10)</td>
<td>11 (16)</td>
<td>6 (10)</td>
<td>3 (5)</td>
<td>6 (8)</td>
<td>.04</td>
</tr>
<tr>
<td>ICU length of stay, median (IQR), d</td>
<td>10 (6-17)</td>
<td>9 (6-15)</td>
<td>9 (6-17)</td>
<td>8 (4-12)</td>
<td>8 (5-12)</td>
<td>8 (4-12)</td>
<td>9 (5-14)</td>
<td>9 (6-14)</td>
<td>.26</td>
</tr>
</tbody>
</table>

Abbreviations: COPD, chronic obstructive pulmonary disease; CPE, cardiogenic pulmonary edema; ICU, intensive care unit; IQR, interquartile range; LOD, Logistic Organ Dysfunction Score; SAPS, Simplified Acute Physiology Score.

*SAPS II is an ICU severity score that includes 15 physiologic, demographic, and underlying disease variables recorded within 24 hours after ICU admission. SAPS II values range from 0 to 163 points. The higher the score, the more severe the illness. The LOD score assesses dysfunction in 6 organ systems: respiratory, cardiovascular, renal, hematologic, hepatic, and neurologic. LOD scores range from 0 to 22 points. The higher the score, the more severe the illness.
incorporate the outcome from long-term facilities or other hospitals, to which some patients were transferred, which limits their significance. The median length of ICU stay was significantly shorter for patients treated with NIV than for patients treated with invasive mechanical ventilation (10 days; IQR, 5-17 days vs 8 days; IQR, 5-12 days, respectively, \( P = .02 \)). Overall, NIV was used for 313 patients (65%), among whom 35 (11%) eventually required endotracheal intubation and CMV. The rate of ICU-acquired pneumonia progressively decreased from 20% in 1994 to 8% in 2001 (\( P = .04 \)). Among the 35 cases of NIV failure, ICU-acquired pneumonia occurred in 17 patients (49%), whereas the incidence of ICU-acquired pneumonia was 11% in the overall population. Among the 166 invasively ventilated patients, neither trends in mortality, SAPS II, LOD score, or age varied significantly over the 8 years. Clinical variables associated with mortality in the univariate analysis are shown in Table 2. These included the SAPS II and the LOD score, ICU-acquired infections and pneumonia, use of NIV, administration of bronchodilators, and year of admission. In the covariate-adjusted logistic regression analysis, the use of NIV, occurrence of ICU-acquired infection, and SAPS II were identified as independently associated with ICU outcome (Table 3). The risk of death was 3-fold lower in patients with COPD or CPE who had received NIV (adjusted OR, 0.39; 95% CI, 0.19-0.81), whereas a high SAPS II and occurrence of nosocomial infection were independently associated with increased mortality.

The mean propensity score, reflecting the probability of each patient receiving NIV, was 0.65 (range, 0.04-0.98). The cohort was divided into quintiles based on the propensity to receive NIV (Table 4). The probability that a patient would receive NIV (as opposed to CMV) increased from quintile 1 to quintile 5. Patients within a quintile were similar in their likelihood to receive NIV. As a validation of the propensity score, the balance of all covariates within each quintile was examined. The prevalence of all covariates was consistent between NIV and CMV groups within each quintile. After entering the propensity score into the stepwise logistic regression model along with the other covariates, results were comparable to those described above, especially regarding the effects of NIV use on mortality (Table 3).

**COMMENT**

This study describes the secular trends in ICU mortality over an 8-year period for patients admitted with acute exacerbation of COPD and severe CPE. We speculate that an improvement in the delivery of NIV over time is associated with a reduction in mortality and nosocomial infections. After adjustment for risk factors for death, NIV was independently associated with a better outcome, whereas a high severity score and occurrence of nosocomial infection were associated with death.

No change over the 8 years occurred in the therapeutic management of these patients except for the use
By contrast, constant educational efforts about administering NIV have been made in the ICU and in the hospital, including implementation of annual training sessions and elaboration on and distribution of recommendations for physicians and nursing staff. Our cohort study’s demonstration of a gradual increased utilization of NIV in our population suggests that a learning curve exists for the practice of NIV in our patient population. Figure 1 suggests that this increasing use of NIV was associated with an improved overall quality of care, likely explaining the decrease in mortality.

Limitations of observational retrospective studies include a possible role of confounding factors, especially changes in medical practice over years, and the difficulty of recording data, including the risk of missing data. We included a propensity score for NIV use in our analysis to minimize bias in the estimate of the effect of NIV on outcome of patients. Inclusion of a propensity score as a covariate in a multivariable regression theoretically normalizes the likelihood of treatment (in this case, noninvasive ventilation) and may effectively adjust for unobserved confounding and selection bias, thereby refining regression estimates. Severity scores and diagnosis of infections were recorded prospectively over these years, without changes in the permanent medical staff over the study period. Not all patients with COPD received bronchodilator therapy with β-stimulants or anticholinergic agents. Studies of patients with severe respiratory acidosis admitted in the ICU are scarce, however, and there are no data to show that the use of bronchodilators could influence mortality trends with noninvasive ventilation.
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ence the admission rate to the ICU, the endotracheal intubation rate, or the ICU fatality rate. Also, several medical or technical issues may explain why beyond randomized clinical trials NIV is not often used for patients in the ICU. Although the use of bronchodilator therapy could be considered suboptimal, the lack of change over the years indicates that this would unlikely influence the results. The relatively modest use of antibiotics is explained by an unchanged restrictive antibiotic policy for these patients in the ICU.

Our study indicates that NIV can be successfully applied outside of a randomized controlled trial setting and potentially achieve similar reductions in mortality. Benefits in reduced mortality have been clearly demonstrated in clinical trials, but it is important to evaluate whether the benefits observed in trials can be translated and confirmed in daily practice. The results of carefully conducted, concealed but nonblinded studies, evaluating a selected group of patients, may not always be replicated during routine application of such a technique. Furthermore, in a few studies, no benefit of NIV could be demonstrated.

One limitation of the randomized controlled trials is the selection of a population in which the likelihood of observing the impact of a new treatment is greater than in the general population. In the study by Brochard et al., approximately 35% of all patients admitted with exacerbated COPD were enrolled. Also, the nonblinded nature of mechanical-ventilation trials makes such trials less rigorous by nature. The results of our cohort study and the progressive reduction of ICU mortality over the 8-year period thus strongly support a beneficial effect of NIV in this population. Chronic obstructive pulmonary disease is a deadly disease with a poor short-term prognosis after hospital admission. Management of acute exacerbation of COPD with NIV is the first treatment that constitutes a major therapeutic advance.

Reduction of nosocomial infections contribute to the consistent reduction in mortality associated with the use of NIV. Nosocomial infections are associated with an increase in morbidity and mortality in ICU patients. Several studies have suggested that NIV was associated with a reduction in the rate of nosocomial infections. In a matched case-control study, we previously have shown that, compared with invasive mechanical ventilation, the use of NIV was associated with a decrease in nosocomial pneumonia, urinary tract infections, and catheter-associated bacteremia. The present cohort comprises 100 patients (21%) included in this previous study. It is noteworthy that rates of nosocomial pneumonia and mortality in this large cohort of patients receiving NIV (11% and 12%, respectively) are very similar to those reported in our previous study (15% and 15%, respectively).

Not using an endotracheal tube that bypasses the upper airways is likely the major reason for the reduction in nosocomial pneumonia during NIV. Studies have also shown that using NIV instead of invasive mechanical ventilation was associated with a reduced use of invasive devices, including intravenous and urinary catheters. Although not specifically addressed in this study, it is very likely that the use of NIV among our patients was associated with a less invasive management overall.

One striking result of this study is that it takes a relatively long time to observe a steady rate for the routine use of NIV and to observe an impact on patient outcome. The effect on mortality parallels the utilization rate of the technique and likely reflects a learning curve effect. Early reports of NIV described the technique as time-consuming for the personnel. Several studies showed that the total workload was not modified over the whole ICU stay, but that there was a specific increase in the workload in the first 6 to 8 hours of delivery of NIV compared with a standard approach. In a randomized controlled trial performed in pneumology wards, Plant et al. trained the teams for a mean of 8 hours in the 3 months preceding the study with an additional monthly hour once the study had started. The specific aspects of NIV to be taught include interaction with a nonsedated dyspneic patient, management of the patient-ventilator interface, monitoring and management of air leaks, and monitoring of parameters reflecting the efficacy of the treatment. Whether the results of this study can be extended to other indications of NIV is unknown. We restricted the study to COPD and CPE because other indications remained more controversial until recently and that it may be too soon to demonstrate a similar effect or are of questionable benefit. It is likely, however, that the increasing number of indications increases the opportunity for the personnel to become familiar with the technique in general, which may also benefit indirectly patients with COPD. Demonstration of the benefit of NIV in selected patients with hypoxemic respiratory failure, in immunosuppressed patients and in other specific groups has markedly increased the utilization rate of this technique.

In addition, the lack of benefits of continuous positive-airway pressure in patients with acute lung injury tends to homogenize the modes of ventilation for all patients.

In conclusion, our study reports that a progressive increase in the use of NIV for patients with acute exacerbation of COPD or severe CPE was associated with a sustained reduction in mortality over the years in the ICU, which may be explained by a reduced rate of complications usually associated with conventional mechanical ventilation, including nosocomial infections.

Author Contributions: Dr Girou had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Girou, Brun-Buisson, Lemaire, Brochard. Acquisition of data: Girou, Tallié. Analysis and interpretation of data: Girou, Brun-Buisson, Brochard. Drafting of the manuscript: Girou, Brun-Buisson, Tallié, Brochard. Critical revision of the manuscript for important in-
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