Outcomes of Noninvasive Ventilation for Acute Exacerbations of Chronic Obstructive Pulmonary Disease in the United States, 1998–2008

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Rationale: The patterns and outcomes of noninvasive, positive-pressure ventilation (NIPPV) use in patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease (COPD) nationwide are unknown.

Objectives: To determine the prevalence and trends of noninvasive ventilation for acute COPD.

Methods: We used data from the Healthcare Cost and Utilization Project's Nationwide Inpatient Sample to assess the pattern and outcomes of NIPPV use for acute exacerbations of COPD from 1998 to 2008.

Measurements and Main Results: An estimated 7,511,267 admissions for acute exacerbations occurred from 1998 to 2008. There was a 462% increase in NIPPV use (from 1.0 to 4.5% of all admissions) and a 42% decline in invasive mechanical ventilation (IMV) use (from 6.0 to 3.5% of all admissions) during these years. This was accompanied by an increase in the size of a small cohort of patients requiring transition from NIPPV to IMV. In-hospital mortality in this group appeared to be worsening over time. By 2008, these patients had a high mortality rate (29.3%), which represented 61% higher odds of death compared with patients directly placed on IMV (95% confidence interval, 24–109%) and 677% greater odds of death compared with patients treated with NIPPV alone (95% confidence interval, 475–948%). With the exception of patients transitioned from NIPPV to IMV, in-hospital outcomes were favorable and improved steadily year by year.

Conclusions: The use of NIPPV has increased significantly over time among patients hospitalized for acute exacerbations of COPD, whereas the need for intubation and in-hospital mortality has declined. However, the rising mortality rate in a small but expanding group of patients requiring invasive mechanical ventilation after treatment with noninvasive ventilation needs further investigation.

Keywords: COPD; positive-pressure ventilation; artificial respiration; epidemiology

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Noninvasive positive pressure ventilation has been shown to improve health-related outcomes in patients with acute exacerbations of chronic obstructive pulmonary disease.

What This Study Adds to the Field

This study provides nationally representative data on trends and outcomes associated with noninvasive positive pressure ventilation and invasive mechanical ventilation for chronic obstructive pulmonary disease–related hospitalizations.

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States and is projected to become the third leading cause of death by 2020 (1, 2). A large proportion of morbidity and mortality from COPD results from acute exacerbations, which lead to 1.5 million emergency room visits and 750,000 hospitalizations annually in the United States (3, 4). Therefore, to improve outcomes and reduce mortality due to COPD, we need to optimize the management of acute exacerbations (5), including the correct use of respiratory support modalities to treat patients with respiratory failure.

Over the last decade, noninvasive, positive-pressure ventilation (NIPPV) has started playing an increasingly important role in the treatment of respiratory failure due to acute exacerbations (6–12). This is because clinical trials demonstrate good efficacy for NIPPV in reducing risk of intubation and mortality, health care providers are becoming increasingly confident with its use, and unlike IMV, it can be implemented outside the ICU, freeing up ICU beds. Therefore, it appears likely that NIPPV use will continue to increase in the coming years.

Although NIPPV use has increased in recent years, to our knowledge, no studies have determined how NIPPV has affected the outcomes of patients hospitalized with acute exacerbations of COPD. An unexpected consequence of the increased familiarity and greater availability of NIPPV may be that it is now used more broadly, potentially including patients who would have not been included in randomized clinical trials. For example, in a landmark trial where Brochard and colleagues showed that NIPPV was effective at reducing mortality among patients with respiratory failure due to acute exacerbations, 67% of screened participants were excluded for a variety of reasons (13). The objective of this study was to examine patterns and outcome of NIPPV treatment for acute exacerbations during 1998–2008 in a large nationally representative sample. Some of the results of this study have been previously reported in the form of an abstract (14).

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MATERIALS AND METHODS

Patient Cohort

We used data from the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project (HCUP-NIS) from 1998 to 2008 (15). Since 1988, HCUP-NIS has collected patient-level clinical and resource use data included in the discharge abstract on about 5 to 8 million inpatient hospital stays from close to a 1,000 hospitals. This represents an approximately 20% stratified probability sample of all United States acute-care, nongovernmental hospitals each year.

Definitions

COPD exacerbation. We included patients ≥ 35 years of age admitted with a primary diagnosis of COPD (ICD-9 codes 490–492 and 495–496) or a primary diagnosis of respiratory failure (ICD-9 codes 5188, 5185, 7991, and 78,609) with a secondary diagnosis of COPD.

Type of respiratory support. Use of NIPPV and IMV was determined based on procedure codes 93.90 and 96.04, respectively. For each in-hospital day up to Day 14, only one of these two procedure codes could be entered into a patient's medical record. Patients were classified as "initially on NIPPV" if they were placed on NIPPV before any other form of respiratory support and as "initially on IMV" if they received IMV before any other form of respiratory support. Patients were said to have transitioned from NIPPV to IMV if IMV was used after NIPPV use.

Other variables. Geographic location was defined as Northeast, Midwest, West, and South based on United States census regions. Hospitals located in a metropolitan area (defined as a population $\geq 500,000$) were classified as urban, whereas others were classified as rural. Urban hospitals were further classified as teaching or nonteaching hospitals.

Presence and classification of comorbidities was based on each patient's secondary diagnoses. Comorbidities were extracted using HCUP comorbidity software (Version 3.2; HCUP, Rockville, MD) (16). Comorbidities that were reported in at least 1% of patients and were clinically relevant were included in our analysis.

Data Analysis

We first examined changes in the frequency of NIPPV and IMV use from 1998 to 2008 and compared patient demographics, income status, payer type, hospital region, and hospital type between patients initially treated with NIPPV, IMV, or no respiratory support after hospital admission.

We examined three outcomes of the hospitalization: in-hospital mortality, length-of-stay, and total charges for the hospitalization. These outcomes were compared between patients receiving NIPPV, IMV, or no respiratory support. The analysis of in-hospital mortality was adjusted for sex, age group, income, payer type, hospital region and type, and relevant comorbidities reported in at least 1% of the cohort using multivariate regression models. Race was excluded from this multivariate model because it was missing for a significant proportion of admissions. In sensitivity analysis, where race was added to the multivariate model, there was no notable change in model parameters (data not shown).

All analyses were performed using Stata version 11 (StataCorp LP, College Station, TX) using discharge weights and strata provided by HCUP-NIS. Because of the large sample size, *P* values for all comparisons were less than 0.001 and are therefore not reported individually.

RESULTS

Patterns of NIPPV and IMV use

During 1998–2008, the number of hospitalizations for acute exacerbations per year remained relatively constant (yearly mean, 765,067; 95% confidence interval [CI], 764,360–765,773), leading to a total of 7,511,267 admissions during 1998–2008, of which 612,650 (8.1%) required respiratory support. From 1998 to 2008, a progressive increase in the use of NIPPV and a decrease in the use of IMV occurred, and by 2008, NIPPV had overtaken IMV as the most frequently used form of respiratory support for

patients hospitalized with acute exacerbations in the United States (Figure 1).

A comparison of patients initially treated with IMV, NIPPV, or no respiratory support revealed that they were mostly similar in their demographic characteristics and comorbidities (Table 1). However, due to temporal differences in the age of patients treated with IMV or NIPPV, data on age are represented separately in Figure 2. This comparison reveals that, among patients initially placed on NIPPV, there was an increase over time in the proportion over 75 years of age, unlike IMV, where the proportion over 75 years of age declined year by year.

Outcomes

In-hospital mortality. There was a steady decline over time in overall in-hospital mortality and in mortality among patients not requiring respiratory support, patients initially treated with IMV, and patients initially treated with NIPPV without a subsequent need for IMV (Figure 3). Contrary to these favorable trends, mortality was high and increased over time in patients needing to be transitioned from NIPPV to IMV (Figure 3). By 2008, these patients had the highest mortality rate among all groups ($\sim 30\%$) (Figure 3). The percentage of patients transitioned from NIPPV to IMV did not increase from 1998 to 2008 ($\sim 5\%$ of those treated with NIPPV each year). However, the absolute number increased rapidly because of the rapid increase in the total number of patients being treated with NIPPV (Figure 4).

Compared with those who survived, patients who died were older, were more frequently white, and were more likely to be on Medicare (Table 2). Among patients who died after being transitioned from NIPPV to IMV, the proportion older than 75 years of age increased over time, and by 2008, more than 50% of these nonsurvivors were older than 75 years of age (Figure 5). A smaller increase in age was also present among those who died after treatment with NIPPV alone.

Adjusted odds ratios for mortality in patients treated with NIPPV with and without transition to IMV, compared with patients treated with IMV alone, are summarized in Figure 6 for each year. The inclusion of sex, age group, payor, hospital

Figure 1. Temporal trends in the use of noninvasive positive pressure ventilation (NIPPV) and invasive mechanical ventilation (IMV) as the initial form of respiratory support in patients hospitalized with acute exacerbations of chronic obstructive pulmonary disease (COPD) in the United States, 1998–2008.

TABLE 1. CHARACTERISTICS OF PATIENTS NOT REQUIRING RESPIRATORY SUPPORT, INITIALLY TREATED WITH NONINVASIVE POSITIVE PRESSURE VENTILATION OR INVASIVE MECHANICAL VENTILATION, DURING HOSPITALIZATION FOR ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE, 1998–2008

	No Respiratory Support during Hospitalization	Initially on IMV	Initially on NIPPV
N (%)	6,898,617 (92%)	404,321 (5%)	208,330 (3%)
Sex, %			
Male	44	47	44
Female	56	53	56
Race/ethnicity, %*			
White	84	80	81
Black	9	12	11
Hispanic	5	5	4
Other	3	3	4
Age group, yr			
35–44	3	2	2
45–54	10	9	10
55–64	20	24	25
65–74	30	34	33
75–84	28	25	24
≥85	9	6	6
Income quartile, %			
1 (lowest)	9	9	7
2	35	30	27
3	28	29	28
4 (highest)	29	32	38
Payor type, %			
Medicare	71	70	71
Medicaid	8	9	10
Private	16	16	17
Other	4	4	3
Hospital region, %			
Northeast	19	20	31
Midwest	22	19	18
South	45	44	33
West	14	18	18
Hospital type, %			
Rural	26	15	19
Urban			
Nonteaching	45	49	42
Teaching	29	36	39
Comorbidities, %†			
Congestive heart failure	25	25	25
Other chronic lung disease	15	14	16
Obesity	7	7	7
Valvular disease	5	5	5
Renal failure	4	4	4
Pulmonary vascular disease	6	6	6
Solid tumor, no metastases	3	3	3

Definition of abbreviations: IMV = invasive mechanical ventilation; NIPPV = noninvasive positive pressure ventilation.

* Twenty-seven percent of the data on race was missing.

† Selected comorbidities as listed.

region, hospital location and teaching status, and comorbidities had little effect on the odds ratios. For example, in 2008 the unadjusted odds ratio for death comparing those transitioned from NIPPV to IMV versus treated with initially with IMV was 1.63 (95% CI, 1.27–2.07), while the fully adjusted odds ratio was 1.61 (95% CI, 1.24–2.09). After 2000, compared with patients initially treated with IMV, the odds ratio for death in patients transitioned from NIPPV to IMV remained above 1. In 2001, there was a sharp increase in the risk of death, followed by a downward correction in 2002 and then an increase toward 2007–2008. In 2008, a patient requiring IMV after NIPPV use had 61% greater odds of death compared with patients directly placed on IMV (95% CI, 24–109%) and 677% greater odds of death compared with a patient treated with NIPPV without transition to IMV (95% CI, 475–948%). Overall, the risk of death among those treated with NIPPV alone (Figure 6, *solid line*) versus those requiring transition from NIPPV to IMV

(Figure 6, *dotted line*) appeared to be diverging away from each other over time.

Charges for hospitalization. Charges for hospitalizations for acute exacerbations increased for all patients from 1998 to 2008. The increase was the steepest and the charges the greatest for patients who were transitioned from NIPPV to IMV (Figure 7).

Length of stay. The length-of-stay decreased gradually among all patients, except for those transitioned from NIPPV to IMV, in whom length-of-stay was the longest and did not decline over time (Figure 8).

DISCUSSION

We performed the first examination of the patterns and outcomes of NIPPV treatment for acute exacerbations of COPD in clinical practice nationwide, using data from an estimated 7,511,267 million hospital admissions in the United States during

Figure 2. Proportion of patients treated with noninvasive positive pressure ventilation (NIPPV), invasive mechanical ventilation (IMV), or without respiratory support for acute exacerbation of chronic obstructive pulmonary disease in the United States during 1998–2008 who were over 75 years of age.

1998–2008. A more than 4-fold increase in NIPPV use, accompanied by a significant drop in the use of IMV, occurred during these years. By 2008, NIPPV was used more frequently to support these patients than IMV. Although the proportion of patients requiring transition from NIPPV to IMV during the hospitalization remained stable at around 5%, the absolute number of such patients expanded rapidly year by year due to the increase in NIPPV use. These patients experienced the highest in-hospital mortality and the most expensive and longest hospitalizations. The mortality in this group appeared to be worsening over time, and by 2008, these patients had 61% higher odds of death compared with patients directly placed on IMV (95% CI, 24–109%) and 677% greater odds of death compared with patients treated with NIPPV alone (95% CI, 475–948%). With the exception of patients transitioned from NIPPV to IMV, in-hospital outcomes were favorable and improved steadily over time in other patients.

The current study, to our knowledge, is the first to report a dramatic shift toward NIPPV use for treating respiratory failure from acute exacerbations in the United States. This is consistent with the results reported by investigators in smaller studies, describing increased use of NIPPV among their patients hospitalized with acute exacerbations (17–19). A variety of factors have likely contributed to this trend. First, since 1993, a number of clinical trials have consistently reported that NIPPV is efficacious in reducing the need for IMV and in-hospital mortality. Second, health care providers are becoming more confident with using NIPPV and have expanded its application beyond those defined in clinical trials (i.e., acute exacerbations in patients between 60 and 70 yr of age) (20) to include patients with an intact sensorium (21) and arterial CO₂ between 55 and 75 mm Hg (22, 23). A recent study has suggested that even patients acutely decompensating with an acute exacerbation in the ICU be given a trial of NIPPV first (24). Last, unlike IMV, NIPPV can be implemented outside the ICU, which is advantageous because of the chronic shortage of ICU beds at many medical centers. Some hospitals have therefore created special nursing units, commonly located next to the ICU, to facilitate NIPPV use (25). The tremendous increase in

Figure 3. In-hospital mortality among all comers (patients not requiring respiratory support, patients treated with invasive mechanical ventilation [IMV], and patients treated with noninvasive positive pressure ventilation [NIPPV]) with and without the need for subsequent transition to IMV for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998–2008. The *P* values for trend in mortality among all the different groups included in the figure were statistically significant ($P < 0.01$).

NIPPV use nationwide highlights the importance of training healthcare providers on the correct use of NIPPV, which requires different expertise and equipment compared with traditional invasive mechanical ventilation. It also underscores our confidence in modes of noninvasive ventilation and the potential for

Figure 4. The number of patients and the number of in-hospital deaths among patients requiring transition from noninvasive positive pressure ventilation (NIPPV) to invasive mechanical ventilation (IMV) after admission for acute exacerbation of chronic obstructive pulmonary disease, 1998–2008.

TABLE 2. COMPARISON OF SURVIVORS AND NONSURVIVORS STRATIFIED BY TREATMENT WITH DIFFERENT TYPES OF RESPIRATORY SUPPORT DURING HOSPITALIZATION FOR ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE, 1998–2008

	Initially on IMV		Initially on NIPPV			
	Survivors	Nonsurvivors	No transition to IMV (95.3%)		Transitioned to IMV (4.6%)	
			Survivors	Nonsurvivors	Survivors	Nonsurvivors
<i>N</i> (%)	311,556 (77%)	91,672 (23%)	180,939 (91%)	17,436 (9%)	7,086 (73%)	2,595 (27%)
Sex						
Male	45	51	45	42	44	44
Female	55	49	55	58	56	56
Race/ethnicity*						
White	79	82	74	81	82	90
Black	13	10	15	14	12	6
Hispanic	5	5	7	3	4	2
Other	3	3	5	2	3	3
Age group, yr						
35–44	2	1	2	<1	3	1
45–54	9	3	8	8	10	2
55–64	24	15	31	26	25	11
65–74	36	36	34	27	35	36
75–84	24	35	22	33	22	38
≥85	5	10	3	7	5	12
Income quartile						
1 (lowest)	9	8	9	4	7	6
2	31	29	26	27	27	25
3	29	29	30	32	28	28
4 (highest)	31	34	35	37	37	42
Payor type						
Medicare	69	79	63	78	70	85
Medicaid	10	6	13	5	11	3
Private	17	11	21	15	17	10
Other	4	3	2	2	3	2
Hospital region						
Northeast	23	27	36	42	37	38
Midwest	12	10	7	2	11	10
South	45	46	37	33	34	33
West	20	17	20	22	19	19
Hospital type						
Rural	13	11	11	7	15	18
Urban						
Nonteaching	51	53	44	47	45	43
Teaching	36	36	45	46	39	39

Definition of abbreviations: IMV = invasive mechanical ventilation; NIPPV = noninvasive positive pressure ventilation.

*Twenty-seven percent of the data on race was missing.

application of newer and better noninvasive ventilation devices in clinical practice.

Our results support the efficacy of NIPPV in reducing the risk of IMV reported in clinical trials in routine clinical use. We found that as NIPPV use increased, the number of patients requiring intubation on IMV dropped by almost half. It appears unlikely that this concomitant rise in NIPPV and drop in IMV use was coincidental and was the result of alternative factors, such as an unexpected drop in severity of exacerbations during later years. To a lesser extent, our data also support the efficacy of NIPPV in reducing in-hospital mortality. As NIPPV use increased, overall in-hospital mortality decreased. However, there was also a decline in mortality among patients treated only with IMV or without any respiratory support, which suggests that the improvement in mortality could partly have resulted from better general medical care rather than the increase in NIPPV use.

The concerning finding in our analysis was the high mortality in the group of patients who, despite initial treatment with NIPPV, required subsequent placement on IMV. Previous studies have reported that (1) high acuity of illness (i.e., significant impairment in level of consciousness) (24), severe acidosis (pH < 7.25) (26, 27), high APACHE II score (28), high SAPS score (24), the presence of complications from sepsis (24), and functional limitations before admission to the ICU (29) and (2)

failure to demonstrate an early response to NIPPV (i.e., no improvement in pH, PaCO₂, and level of consciousness within 1 hour of initiation of NIPPV) (30) characterize patients likely to require IMV if initially treated with NIPPV. Therefore, two explanations might explain the high mortality rate in patients requiring IMV after NIPPV: (1) increasing the use of NIPPV in patients who are difficult to ventilate (29) and (2) continuation of NIPPV despite a lack of early improvement. However, our study does not provide concrete evidence to confirm or refute either of these explanations. The decline in mortality among patients treated with IMV over time identified in our study (see Figure 3) supports the first explanation because increasing the use of NIPPV rather than IMV to treat sick and difficult-to-ventilate patients should lead to a decline in mortality among patients with IMV alone.

The group of patients transitioned from NIPPV to IMV represents a small fraction (~ 5%) of patients placed on NIPPV each year. It is difficult to compare this rate of transition with that reported in other studies because of differences in study design (observational vs. clinical trial), severity of illness in included patients (severe versus mild exacerbation), and level of monitoring (intensive care versus general medical ward). For example, in an observational study that only included ICU patients, Phua and colleagues reported that 16% of their cohort

Figure 5. Proportion of those who survived or died after treatment with noninvasive positive pressure ventilation (NIPPV) with and without the need for subsequent transition to invasive mechanical ventilation (IMV) due to acute exacerbations of chronic obstructive pulmonary disease during 1998–2008 who were older than 75 years of age.

required transition from NIPPV to IMV (28). In contrast, in a clinical trial among patients treated in a general medical ward, del Castillo reported the same rate of transition from NIPPV to IMV as in our study (5%) (31). There are a number of possible explanations for this low rate of IMV use after NIPPV, which would be best investigated in a prospective study: (1) a number of patients could have made an end of life decision to not accept IMV, (2) patients could have died before IMV could be started, or (3) clinicians did a good job of selecting appropriate patients for NIPPV, resulting in a low requirement for subsequent IMV.

Irrespective of the reason, 5% is a small proportion, and some may argue that from a societal perspective the higher mortality in this group is acceptable because our increased and aggressive use of NIPPV has been associated with a significant reduction in the use of IMV and overall in-hospital mortality. However, NIPPV was introduced as a treatment option because it reduces the risk of IMV; therefore, it is difficult to justify higher mortality from NIPPV than from IMV in any individual patient. Also, although the proportion of patients requiring transition from NIPPV to IMV has remained stable, the absolute number of patients, the absolute risk of death, and the risk of death relative to patients treated with IMV or not needing respiratory support has increased over time. Finally, evidence suggests that this phenomenon may not be limited to patients with acute exacerbations of COPD. For example, Esteban and colleagues reported that, in a study examining treatment options for an unselected population of patients doing poorly after extubation in the ICU, those who failed NIPPV and required reintubation experienced higher mortality than patients managed with standard medical therapy and requiring reintubation (32).

Our finding of increased mortality among patients transitioned from NIPPV to IMV is contrary to that found in the carefully monitored patient environment of clinical trials, where those transitioned from NIPPV to IMV did not have higher mortality than patients placed on IMV from the beginning (24, 33). Based on the results of these clinical trials, investigators have previously recommended a trial of NIPPV even for patients with advanced decompensation due to an acute exacerbation

Figure 6. Multivariable analysis of in-hospital mortality compared with primary invasive mechanical ventilation (IMV) among patients treated with noninvasive positive pressure ventilation (NIPPV) with and without subsequent transition to IMV for acute exacerbation of chronic obstructive pulmonary disease, 1998–2008. Multivariate analyses are adjusted for sex, age group, income, payor, hospital region, hospital location and teaching status, and the presence of each comorbidity listed in Table 1.

(24). Our results from routine clinical practice, however, suggest the use of caution with using NIPPV among patients at high risk of requiring subsequent IMV, unless they are intensively monitored by an experienced team, and that there should be a plan to intervene early if there is no improvement. Another observational study, performed in French ICUs, has reported that patients transitioned from NIPPV to IMV did not have increased mortality (34). However, the study included patients with causes of respiratory failure besides COPD exacerbation, such as cardiogenic pulmonary edema, making it difficult to compare their results to ours.

Figure 7. Charges for hospitalization for acute exacerbation of chronic obstructive pulmonary disease grouped by type or respiratory support used, 1998–2008. IMV = invasive mechanical ventilation; NIPPV = noninvasive positive pressure ventilation.

Figure 8. Length-of-stay in days for patients admitted with acute exacerbations of chronic obstructive pulmonary disease grouped by type or respiratory support used during the hospitalization, 1998–2008. IMV = invasive mechanical ventilation; NIPPV = noninvasive positive pressure ventilation.

Our study has several limitations. Although it includes a large nationally representative sample of patients hospitalized with acute exacerbations, it does not include information on the severity of the exacerbation, response to NIPPV treatment, end-of-life decision-making, or the location of the patient in the hospital (intensive care, general medical ward, etc.), which would allow a more detailed examination of predictors of NIPPV failure and death. Also, similar to prior studies, we used ICD-9 codes to identify patients with acute exacerbations, and, despite their validation, they have well recognized limitations on their accuracy (35). Finally, although procedure codes for NIPPV and IMV use are likely to be more reliable than ICD-9 codes are for the underlying diagnosis, they have not been directly validated by us.

In conclusion, our study demonstrates that NIPPV use increased rapidly to treat acute exacerbations of COPD among hospitalized patients in the United States during 1998–2008. This increase in the use of NIPPV was associated with declines in the number of patients requiring invasive mechanical ventilation and in mortality. Healthcare providers should continue to be aggressive with the use of noninvasive ventilation for patients with acute exacerbations but should intensively monitor sick patients, intervene early in the absence of improvement, and carefully examine if transition to IMV is in the interest of a patient with a poor prognosis who has just failed NIPPV because our data suggest that patients who fail NIPPV and subsequently require IMV experience significantly higher mortality than patients placed on IMV from the beginning and experience the longest and most expensive hospitalizations for COPD exacerbations.

Author disclosures are available with the text of this article at www.atsjournals.org.

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