CHEST

Original Research

CRITICAL CARE MEDICINE

Epidemiology and Outcomes of *Clostridium difficile*-Associated Disease Among Patients on Prolonged Acute Mechanical Ventilation

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Purpose: **Patients receiving prolonged acute mechanical ventilation (PAMV), although comprising a third of all mechanical ventilation (MV) patients, consume two-thirds of all the resources allocated to MV, and their numbers are projected to double by 2020. By virtue of their prolonged hospital length of stay (median LOS, 17 days), they are subject to such nosocomial infections as *Clostridium difficile*-associated disease (CDAD), the incidence and age-adjusted case fatality rate of which doubled between 2000 and 2005. We examined the rates and outcomes of CDAD among adult PAMV patients.**

Methods: **We analyzed 2005 data from the Health Care Utilization Project/Nationwide Inpatient Sample from the Agency for Healthcare Research and Quality. PAMV and CDAD were identified using the *International Classification of Diseases*, ninth revision, clinical modification codes 96.72 and 008.45, respectively.**

Results: **Among 64,910 adult PAMV patients who were discharged in 2005, 3,468 patients (5.34%) had a concurrent diagnosis of CDAD (PAMV patients who were discharged with concomitant diagnosis of CDAD [CDAD+]). CDAD+ patients who were discharged were older (mean [± SD] age, 66.7 ± 15.9 vs 63.7 ± 16.9 years, respectively; $p < 0.001$) and were more likely to have been admitted to the hospital from a long-term care facility (5.7% vs 2.9%, respectively; $p < 0.001$) than PAMV patients who were discharged without CDAD (CDAD−). Although crude hospital mortality rates did not differ among PAMV patients who were discharged from the hospital by CDAD status (CDAD+, 32.6%; CDAD−, 33.0%; $p = 0.598$), both unadjusted calculations and propensity-score adjustment showed a substantial increase in LOS (6.1 days; 95% confidence interval [CI], 4.9 to 7.4) and total costs ($10,355; 95% CI, $7,540 to $13,170) among CDAD+ patients.**

Conclusions: **PAMV patients have an order of magnitude higher risk of having CDAD than other hospitalized patients. Concurrent CDAD infection is associated with increased hospital LOS and costs. The PAMV population is an attractive target for aggressive measures aimed at CDAD prevention.** ***(CHEST 2009; 136:752–758)***

Abbreviations: CDAD = *Clostridium difficile*-associated disease; CI = confidence interval; ICD-9-CM = *International Classification of Diseases,* ninth revision, clinical modification; IQR = interquartile range; LOS = length of stay; MV = mechanical ventilation; NIS = Nationwide Inpatient Sample; PAMV = prolonged acute mechanical ventilation

In the United States, patients requiring prolonged acute mechanical ventilation (PAMV [defined as mechanical ventilation [MV] for ≥ 96 h]) constitute one-third of all hospitalized patients undergoing MV. Despite representing a minority of all patients needing MV, those defined as needing PAMV consume two-thirds of the hospital resources devoted to the care of all MV patients.[1] Annually, hospital costs for PAMV exceed $16 billion, and the median hospital length of stay (LOS) among those patients requiring PAMV is 17 days.[1] The burden of PAMV will rise in the future because projections[2] suggest that the number of PAMV patients discharged from the hospital will double between 2000 and 2020, reaching > 600,000 cases annually. Because of their prolonged hospitalization and likely concomitant exposure to antibiotics,

patients requiring PAMV are at risk for the development of superinfections with organisms such as methicillin-resistant *Staphylococcus aureus* and *Clostridium difficile*-associated disease (CDAD).

C difficile in particular has emerged as an important pathogen responsible for increasing morbidity and mortality.[3] Since 2000, multiple hospital-based outbreaks of a new hypervirulent BI/NAP1/027 strain of *C difficile* have been reported[4,5] in the United States, Canada, and Europe. Advanced age, multiple comorbidities, and clear exposure to antibiotics are traditional risk factors for CDAD, although several reports[6,7] have identified community-acquired CDAD among populations of children, pregnant women, and other groups without these risk factors. Reflective of this changing epidemiology is the overall increase in the volume and incidence of hospitalizations with CDAD in the United States among both adults and infants.[3,8]

Among critically ill patients, CDAD is responsible for a 6% incremental increase in the risk of death.[9] Although the epidemiology and outcomes of CDAD in the resource-intensive PAMV population are not well understood, attention to the prevention of nosocomial complications in this population may improve not only clinical but also economic outcomes. We hypothesized that PAMV patients represent a unique cohort of subjects who are at increased risk for CDAD, and that CDAD in those patients with PAMV is associated with greater hospital mortality, LOS, and costs.

Materials and Methods

No human subjects were enrolled specifically in this study. This study was exempt from regulations guiding the protection of human subjects because it is a secondary analysis of a publicly available data set.

Data Source, Cohort, and Case Definitions

We utilized a single year (2005) of data from the Healthcare Costs and Utilization Project/Nationwide Inpatient Sample (NIS) of the Agency for Healthcare Research and Quality. The NIS consists of a stratified sample of hospital discharge records from approximately 1,000 participating facilities, representing about 20% of all community hospitals in the United States. The unit of reporting in this database is a hospital discharge. The NIS database includes data on patient demographics, diagnoses and procedures, in-hospital mortality, as well as hospital charges and LOS for each discharge. Additional data files, linkable to discharges in the NIS database, provide data on hospital characteristics, illness severity measures, and cost-to-charge conversion coefficients for each individual institution in the database. The Agency for Healthcare Research and Quality undertakes an assessment of completeness and data quality, and documentation is provided with the data set.[10]

We identified patients undergoing PAMV based on the presence of the *International Classification of Diseases,* ninth revision, clinical modification (ICD-9-CM) procedure code 96.72 in any discharge diagnosis field. The presence of CDAD was identified using the ICD-9-CM code 008.45 in any discharge diagnosis position.

Outcomes Examined

The primary outcome of interest was hospital mortality. Secondary outcomes were hospital LOS (in days) and hospital costs (in US dollars).

Group Comparisons and Statistical Analysis

We compared outcomes among all PAMV patients who were discharged from the hospital with a concomitant diagnosis of CDAD (CDAD+) to those PAMV patients who were discharged from the hospital without CDAD (CDAD−). We examined demographic, clinical, hospital, and discharge characteristics in these groups. Crude outcomes of CDAD+ hospitalizations were compared with CDAD−. Mean (SD) and median (interquartile range [IQR], 25 to 75%) values were calculated for continuous variables, and counts and proportions calculated for categorical variables. Continuous variables were compared between the two groups using the Student *t* test. Categorical variables were compared using the χ^2 test. All inferences were two tailed. Statistical significance was defined to be present at $\alpha = 0.05$.

To adjust for confounding, we developed propensity score models based on patient demographics (age, race, and gender), patient type (urgent, emergent, elective, and trauma), hospital admission source, weekend hospital admission status, comorbidities (based on the Elixhauser classification[11]), number of discharge diagnoses, and hospital characteristics (*eg*, hospital size and location) [Table 1]. Propensity score matching was conducted using a greedy 5:1 digit algorithm.[12,13] Stratification matching and kernel matching were also conducted to examine the consistency of the estimates via different matching methods.[12–14] We examined both spline terms and medically plausible interactions with age (one age interaction term was ultimately included). The model fit was assessed with the Hosmer-Lemeshow goodness-of-fit and the area under the receiver operating curve. Statistical analyses were performed using a statistical software package (Stata/SE, version 10.1; Stata Corp; College Station, TX).

Results

Of the 64,910 discharges of patients with PAMV in 2005, CDAD was noted in 3,468 (5.3%). Among those patients with CDAD, this represented the

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