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Major Article

Decreased mortality in patients prescribed vancomycin after implementation of antimicrobial stewardship program

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Background: The impact of an antimicrobial stewardship program (ASP) on 30-day mortality rates was evaluated in patients prescribed vancomycin in a Veterans Affairs hospital.

Methods: A retrospective chart review of patients receiving a minimum of 48 hours of vancomycin during October 2006-July 2014. A multivariate logistic regression analysis was used to determine predictors of mortality. Interventions of the ASP consist of appropriate antibiotic selection, dosing, microbiology, and treatment duration.

Results: Death occurred in 12.4% of 453 patients. Of the 56 deaths, 64.3% occurred during prestewardship versus 35.7% during stewardship ($P = .021$). Increased mortality was associated with pre-ASP (odds ratio [OR], 2.17; 95% confidence interval [CI], 1.13-4.27), age (unit OR, 1.08; 95% CI, 1.05-1.12), nephrotoxicity (OR, 3.24; 95% CI, 1.27-8.01), and hypotension (OR, 3.28; 95% CI, 1.42-7.44). Patients treated in the intensive care unit were associated with increased mortality. Patients in the stewardship group experienced lower rates of mortality, which may be caused by interventions initiated by the stewardship team, including minimizing nephrotoxicity and individualized chart review.

Conclusions: Mortality in patients treated with vancomycin was decreased after antimicrobial stewardship was implemented. As anticipated, older age, hypotension, nephrotoxicity, and intensive care unit admission were associated with an increased incidence of mortality.

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A growing body of evidence demonstrates that hospital-based programs dedicated to improving antibiotic use, commonly referred to as antimicrobial stewardship programs (ASPs), can both optimize the treatment of infections and reduce adverse events associated with antibiotic use.[1,2] By concentrating on appropriate antimicrobial use, ASPs have a large impact on decreasing rates of nosocomial infections, rates of resistant pathogens, and antibiotic expenditures.[3] To date, most stewardship literature focuses on process measures, including cost savings, effectiveness, avoidance of adverse drug reactions, and toxicity.[4,5] Additionally, clinical outcomes have been studied to show effectiveness of ASPs through decreases in antimicrobial resistance and infections.[6] There are a limited number of publications discussing the impact of ASPs on mortality, an additional clinical outcome that could be used.[7,8]

Vancomycin, a glycopeptide antibiotic, is a commonly used drug of choice for infections caused by methicillin-resistant *Staphylococcus aureus*. Elimination is primarily through the kidneys; approximately 90% is renally eliminated, unchanged in the urine.[9] Vancomycin has been associated with nephrotoxicity; however, studies have reported the nephrotoxic potential is <5%.[4,9-11] The antibiotic has had considerable data published on pharmacokinetic studies, leading to recommendations to obtain and target serum vancomycin trough concentrations as means of therapeutic effectiveness and to minimize risk of toxicity.[12] Vancomycin is an ideal agent to study given the multitude of potential interventions by an ASP.

There is limited literature on the impact of ASPs on mortality, more specifically regarding association with vancomycin. A review

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of ASP interventions appraised 10 studies that identified mortality as an outcome.[13] Only 1 study out of 10 found a significant reduction in mortality.[14] This highlights the limited data available exploring antimicrobial stewardship interventions.

We aimed to evaluate the impact of an ASP on 30-day mortality rates of patient treated with intravenous (IV) vancomycin therapy at a Veterans Affairs hospital. A secondary outcome was to determine significant risk factors for mortality associated with vancomycin.

MATERIALS AND METHODS

Setting and study design

This was a single-center, institutional review board–approved, retrospective chart review of patients that received IV vancomycin at the Veteran Affairs Western New York Healthcare System, Buffalo, New York. Patients were obtained via medication administration reports of IV vancomycin during the 2 designated time periods of October 1, 2006-July 31, 2008 (pre-ASP) and August 1, 2011-July 31, 2014 (ASP). The time gap between pre-ASP and ASP included a development period of the ASP program during which staffing was inconsistent.

The ASP is a patient-centered design that includes an infectious diseases pharmacist with the support of infectious diseases physicians. The ASP does not use any automated protocols or guidelines; there is individualized chart review, microbiology review, and consultation with an infectious disease physician as needed. Interventions of the ASP consist of prospective audit and feedback, including appropriate antibiotic selection and dosing, microbiology, and duration of treatment. The ASP provides monthly education to medical house staff to educate on antimicrobial stewardship and local antimicrobial resistance patterns. To further limit inappropriate antimicrobial use within the facility, a restricted antibiotic policy is enforced that requires infectious diseases service approval of preselected antimicrobial agents. The restricted antibiotic policy has been in place during the entire study period—both pre-ASP and during ASP.

Study population

Patients included in this study ranged in age from 18-89 years old. Patients were included if they received a minimum of 48 hours of IV vancomycin. Each patient was included only once within the study. Patients were excluded if they had received IV contrast dye within 7 days prior to or during therapy or if they received concomitant vasopressors, cyclosporine, tacrolimus, or amphotericin B. Patients were also excluded if they received chemotherapy within the last 30 days or were on dialysis.

Outcome measures

The primary outcome was to evaluate the 30-day mortality rate in patients that received IV vancomycin therapy. Mortality was assessed via chart review. Secondary outcomes included any significant risk factors for mortality and the impact of the ASP on vancomycin mortality rates. Baseline demographics included age, sex, race, height, weight, body mass index, serum creatinine, RIFLE (Risk, Injury, Failure, Loss of function, End-Stage Renal Disease) criteria,[15] methicillin-resistant *S aureus* colonization nasally, and Charlson Comorbidity Index score.[16] Additional data collection included service admitted to, indication for vancomycin treatment, microbiology cultures, total duration of vancomycin treatment, initial vancomycin trough, and maximum vancomycin trough. Total duration of therapy, total length of stay, and readmission to hospital within 30 days were also collected for each patient included. An initial vancomycin trough concentration was defined as a trough concentration obtained within the first 96 hours of starting vancomycin therapy. Vancomycin trough concentration is a laboratory value of serum concentration of vancomycin obtained 30 minutes prior to a dose of vancomycin. All troughs were taken within 30 minutes of the next scheduled dose of vancomycin. Nephrotoxicity was defined as an increase in serum creatinine of at least 0.5 mg/dL from baseline or a 50% increase from baseline for 2 consecutive days.[12]

Statistics

Descriptive statistics were used to compare patients who died and those that survived and those treated in the pre-ASP and ASP time frames. The χ^2 tests were used for continuous variables. Student *t* test or analysis of variance was used for continuous variables. Significant baseline characteristics ($P < .05$) from each analysis were built into a multivariate logistic regression analysis to determine impact of the ASP on death and to determine predictors of mortality. Nonsignificant factors were removed in a step-wise backward elimination fashion until a stable model for predicting death. Results were presented as odds ratios (ORs) with a 95% confidence interval (CI). Statistical analysis was performed using JMP software version 13 (SAS Institute, Cary, NC).

RESULTS

There were 453 patients treated with a minimum of 48 hours of IV vancomycin therapy during the study period. A total of 226 patients were treated in the pre-ASP time period, and 227 patients were treated during the ASP time period. Indications for treatment with vancomycin included bacteremia; endocarditis; infections from intra-abdominal, genitourinary, and respiratory sources; skin and soft tissue or bone and joint infections; and sepsis with unknown origin.

Death versus survival

There were a total of 56 (12.4%) deaths within 30 days of vancomycin treatment (Table 1). Death was more prevalent in those treated for respiratory infections (53.6% vs 21.9%; $P < .0001$). Death was least common among those patients treated for skin and soft tissue or bone and joint infection (death, 17.9% vs 51.4%; $P < .0001$). All other indications were equivalent statistically. In the prestewardship time frame, endocarditis was more prevalent (9.3% vs 4.4%; $P = .039$). In the stewardship time frame, treatment of sepsis with unknown origin with vancomycin was more prevalent (16.7% vs 8%; $P = .0045$). All other indications were equivalent between the 2 time frames. There were a statistically significant greater number of deaths in the pre-ASP time period of 36 (64.3%) deaths compared with 20 (35.7%) deaths in the ASP time period ($P = .02$).

Patients who died were older (76.2 ± 11.2 vs 67.1 ± 12.6 years; $P < .001$) and had a lower creatinine clearance (63.1 ± 29.7 vs 74.8 ± 32.0 mL/min; $P = .01$). Those patients who died had higher Charlson Comorbidity Index scores, with a median score of 3 (interquartile range, 3-6), than those that survived, with a median score of 2 (interquartile range, 1-3). There were more patients that died who were admitted to the intensive care unit (ICU) (48.2%) than those who survived (17.1%; $P < .0001$). In those patients that died, hypotension was seen in 14 patients (25%) compared with 30 patients (7.6%) in the survival group ($P < .001$). Nephrotoxicity was more prevalent in those patients who died: 11 patients (19.6%) compared with 37 patients (9.3%; $P = .02$).