J Infect Chemother 22 (2016) 671–676

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

Impact of body mass index on clinical outcomes in patients with gram-negative bacteria bloodstream infections

Bryan D. Lizza [a], Nathaniel J. Rhodes [a, b], John S. Esterly [a, c, **], Carolyn Toy [d], Jenna Lopez [d], Marc H. Scheetz [a, b, *]

[a] Department of Pharmacy, Northwestern Medicine, USA
[b] Department of Pharmacy Practice, Midwestern University, USA
[c] Chicago State University College of Pharmacy, Department of Pharmacy Practice, USA
[d] Chicago College of Pharmacy, Midwestern University, USA

ARTICLE INFO

Article history:
Received 15 April 2016
Received in revised form
3 July 2016
Accepted 7 July 2016
Available online 31 August 2016

Keywords:
Bloodstream infections
Sepsis
Obesity
Organ failure
Death

ABSTRACT

Introduction: Excess body mass index (BMI) is associated with a higher risk of death in many disease states, yet less is known about the impact of higher BMIs on clinical outcomes of serious bacterial infections. We sought to quantify the risk of all-cause mortality and/or organ failure following Gram negative bacteria bloodstream infections (GNBSI) according to BMI.

Materials and methods: We retrospectively reviewed the charts of patients with confirmed GNBSI who received ≥48 h of active antimicrobial therapy. Composite and component patient outcomes, including hospital mortality and organ failure, were assessed as a function of BMI. Organ failure was defined using modified consensus Surviving Sepsis Campaign definitions. Multi-variate methods were used to control for baseline confounders.

Results: Seventy-six patients met our inclusion criteria, of whom 8 died (10.5%). The majority of GNBSI were *Escherichia* (41.6%) or *Klebsiella* species (23.3%). Patients with higher BMI more frequently developed cardiovascular failure ($P = 0.032$), respiratory failure ($P < 0.001$), renal failure ($P = 0.003$), and died ($P = 0.009$). Multivariate analyses demonstrated that higher BMIs were associated with a greater risk of death and/or organ failure (aOR 1.07, 95% CI 1.01–1.14), respiratory failure (aOR 1.10, 95% CI 1.03–1.17), and renal failure (aOR 1.08, 95% CI 1.01–1.14) after adjusting for relevant covariates.

Conclusion: Higher BMIs in patients with GNBSIs were associated with a greater risk of a composite of all-cause mortality and organ failure.

1. Introduction

Although the prevalence of obesity in the United States has remained stable, the proportion of adults who are overweight or obese is approximately 70% [1–3]. It is well known that patients with a body mass index (BMI) ≥ 25 kg/m^2 are at a higher risk of complications such as cardiovascular disease, diabetes mellitus, certain cancers, and a substantially higher risk of death by consequence [4,5]. While higher rates of comorbid conditions are known for those of higher BMI, less is known about the impact of BMI on clinical outcomes of infection. Several evaluations have attempted to study the impact of excess BMI on outcomes related to critical illness. Critically ill, obese patients have been shown to exhibit prolonged periods of mechanical ventilation or durations of stay in the intensive care unit (ICU) [6–9]. Critical illness and obesity are also well known to influence antibiotic exposure by mediating drug disposition and clearance, potentially leading to poor clinical outcome in patients with infections. Conversely, several studies of critically ill adult patients have observed a protective effect of higher BMI with respect to mortality – a phenomenon referred to as the "obesity paradox" [10–13]. As such, the overall impact of BMI in patients with acute infection remains unclear at this time [14,15].

* Corresponding author. Department of Pharmacy Practice, Chicago College of Pharmacy, Midwestern University, 555 31st Street, Downers Grove, IL, 60615, USA. Fax: +1 630 515 6958.
** Current affiliation: Merck Research Labs, USA. At the time of writing: a and c.
E-mail address: mschee@midwestern.edu (M.H. Scheetz).

http://dx.doi.org/10.1016/j.jiac.2016.07.006
1341-321X/

2. Patients and methods

2.1. Methods

This was a retrospective, cohort study conducted on patients admitted to Northwestern Memorial Hospital (NMH) in Chicago, IL between January 1, 2012 and December 31, 2012. Clinical and laboratory data were extracted from the medical record by trained study personnel using a standardized data collection tool. Medical records were reviewed to identify patients receiving treatment for a Gram negative bloodstream infection (GNBSI). Patients were included in the analysis if they were ≥18 years of age and received ≥48 h of active antimicrobial therapy directed at the causative pathogen. Patients were excluded from the analysis for age <18 years of age, pregnancy, or incarcerated status. BMI was calculated using height and weight documented in the medical record (and originally measured by a registered nurse participating in the clinical care of the patient). BMI was calculated as an interval variable and was classified according to the World Health Organization clinical criteria for BMI categories as: normal weight (18.5–24.99 kg/m^2), overweight (25.0–29.99 kg/m^2), or obese (30.00–39.99 kg/m^2) [16]. We utilized a modified criterion to categorize morbid obesity as >40.0 kg/m^2 and excluded patients with a BMI <18.5 kg/m^2 on the basis of previous analyses [14,17].

2.2. Microbiology and susceptibility

Organism identification and susceptibility testing were completed for all GNBSI with the Vitek 2 system (bioMérieux, Balmes-les-Grottes, France) or by manual biochemical identification when necessary. Antimicrobial susceptibility testing was performed on all isolates by the Vitek 2 system, as approved by the United States Food and Drug Administration to determine appropriate minimum inhibitory concentrations (MICs). Organism susceptibility was interpreted according to the CLSI interpretive guidelines in place during the study period [18]. All patients in the study had antimicrobials prospectively dosed according to hospital protocols by clinical pharmacists accounting for body weight, renal function and presumed source of infection in accordance with institutional policies. Any deviation from institutional policies within the study was likely random. In cases where multiple Gram-negative species were simultaneously isolated from a blood culture, therapy was deemed active only when all organisms were susceptible to the antimicrobial administered. For patients who developed subsequent bacteremia due to Gram-negative or other bacteria, only the initial event was included. Subsequent infections with the index organism following at least 2 negative blood cultures within the same hospital stay were coded as re-lapse. Infections with a different organism within the same hospital stay were coded as super-infection. The institutional review boards at Northwestern University and Midwestern University approved this study.

2.3. Definitions and clinical variables

ICU-onset infection was defined as patient in the ICU at the time when the culture was obtained. ICU transfer was defined as any admission to the ICU after the time the culture was obtained. Organ dysfunction was assessed any time after the first positive blood culture and definitions were adapted from consensus guidelines: cardiovascular failure was defined as systolic blood pressure <90 mm Hg, mean arterial pressure <70 mm Hg, or the need for vasoactive agents; respiratory failure was defined as the arterial hypoxemia (Pa02/Fi02 < 300) or the need for mechanical ventilation (including noninvasive positive pressure ventilation); renal failure was defined as the presence of acute oliguria (<0.5 mL/kg/hr for at least 2 h) or an increase in creatinine >0.5 mg/dL compared to baseline value obtained within the preceding 6 months. Hematologic failure was defined as non-iatrogenic prolongation of the International Normalized Ratio (INR) > 1.5 or the activated partial thromboplastin time (aPTT) > 60 s. Thrombocytopenia was defined as a platelet count <100,000/μL. Hepatic failure was defined as an increase of the alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than three times the upper limit of normal or a plasma total bilirubin >4 mg/dL [19]. Severity of illness was calculated using a modified form of the Acute Physiology and Chronic Health Evaluation (APACHE) II score on the day of first positive blood culture [20]. In our institution, hydrocortisone may be administered for the treatment of refractory shock at doses of 200–300 mg/day. The most likely source of the bloodstream infection was obtained from the attending physician's written diagnosis. Receipt of active therapy was defined as the use of an antimicrobial agent that the organism was identified as being susceptible to according to CLSI guidelines. Time-to-initiation of active therapy was defined as the time from culture to receipt of an active antimicrobial agent. Time-to-positive culture was defined as the time from culture collection to when the physician was notified electronically or via the medical record according to laboratory documentation. Current or prior immunosuppressant therapy was defined as having received a chemotherapeutic agent for malignancy or to prevent rejection within the previous 90 days.

2.4. Statistical analysis

The primary outcome was the composite endpoint of all-cause mortality and/or organ failure analyzed according to BMI as an interval (i.e. for each increase of 1 kg/m^2) predictor. Secondarily, we analyzed each component of the composite primary outcome (i.e. all-cause mortality, cardiovascular, respiratory, and/or renal failure), hospital and ICU length of stay (LOS) post-culture, total number of days of organ failure, and total days of antimicrobial therapy following the day of culture according to BMI as both interval and categorical predictors.

Data analysis was performed using SPSS Version 21.0 (IBM Corporation, Chicago, IL) and Stata Version 13.0 (Statacorp, College Station, TX). Descriptive analyses were generated for all study variables. Univariate analyses were conducted on each independent variable for the outcomes of interest. Interval data are presented as mean ± standard deviation (SD) unless otherwise noted and were analyzed using either the Students t-test or one way ANOVA, as appropriate. Categorical data are presented as n (%). Either Chi square and Fisher's exact tests were performed, as appropriate, for dichotomous data.

Multivariate models were created when the incidence rate of a dependent outcome observed was at least 10%. Models were designed to evaluate the impact of patient BMI (i.e. the independent variable of interest) on the probability of binary clinical outcomes (e.g. all-cause mortality and organ failure) as dependent variables while controlling for relevant covariates. All independent variables with a plausible relationship to dependent outcomes and a significance level of $P \leq 0.2$ in the univariate analysis were considered in the multivariate model. Modified APACHE II score and BMI were forced into the model. A backwards, stepwise procedure was performed by removing the least significant variable iteratively. The most parsimonious and descriptive model was determined by comparing the number of predictors model and number of predictors model − 1. The difference of two times the change in log-likelihood between the models was required to exceed an objective function value of 3.84 (i.e. one degree of freedom) for acceptance of increased complexity [21]. Goodness of