Obesity and Site-Specific Nosocomial Infection Risk in the Intensive Care Unit*

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Abstract

Background: Obese patients are at higher than normal risk for postoperative infections such as pneumonia and surgical site infections, but the relation between obesity and infections acquired in the intensive care unit (ICU) is unclear. Our objective was to describe the relation between body mass index (BMI) and site-specific ICU-acquired infection risk in adults.

Methods: Secondary analysis of a large, dual-institutional, prospective observational study of critically ill and injured surgical patients remaining in the ICU for at least 48 h. Patients were classified into BMI groups according to the National Heart, Lung and Blood Institute guidelines: ≤ 18.5 kg/m² (underweight), 18.5–24.9 kg/m² (normal), 25–29.9 kg/m² (overweight), 30.0–39.9 kg/m² (obese), and ≥ 40.0 kg/m² (severely obese). The primary outcomes were the number and site of ICU-acquired U.S. Centers for Disease Control and Prevention-defined infections. Multivariable logistic and Poisson regression were used to determine age-, sex-, and severity-adjusted odds ratios (ORs) and incidence rate ratios associated with differences in BMI.

Results: A total of 2,037 patients had 1,436 infection episodes involving 1,538 sites in a median ICU length of stay of 9 days. After adjusting for age, sex, and illness severity, severe obesity was an independent risk factor for catheter-related (OR 2.2; 95% confidence interval [CI] 1.5, 3.4) and other blood stream infections (OR 3.2; 95% CI 1.9, 5.3). Cultured organisms did not differ by BMI group.

Conclusion: Obesity is an independent risk factor for ICU-acquired catheter and blood stream infections. This observation may be explained by the relative difficulty in obtaining venous access in these patients and the reluctance of providers to discontinue established venous catheters in the setting of infection signs or symptoms.

OBESITY IS PERVERSIVE, affecting more than 30% of Americans in all age and socioeconomic groups [1,2]. Its implications include higher risks of cancer, diabetes mellitus, hyperlipidemia, heart disease, hypertension, insulin resistance, and death [3]. Whereas the association between obesity and these chronic conditions is clear, there remains considerable debate regarding the role of obesity in outcomes in the critical care setting and after trauma. A number of authors have documented worse outcomes in obese patients in the critical care setting [4] and after trauma [5–8], but others have been unable to demonstrate differences in outcomes related to obesity [9–13].

Of the reports examining the relation between obesity and outcomes in the intensive care unit (ICU), few have examined infection incidence or outcomes specifically. Boichichio et al. reported a twofold increase in the rates of blood stream, urinary tract, and respiratory infections in obese patients (body mass index [BMI] > 30 kg/m²), but with an obesity rate of only 5.3% in the series, it is difficult to extrapolate these results to populations where the obesity rate is substantially higher. Smith et al. recently reported that obese patients are not at higher risk of death from infection [14] but did not examine infection incidence specifically as it relates to BMI. Our objective was to describe the association be-

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tween obesity and site-specific nosocomial infection rates in critically ill and injured adults. We hypothesized that obese patients would be at higher risk for nosocomial infections at all sites.

Patients and Methods

Study design and participating centers

The study was approved by the Institutional Review Board of Vanderbilt University Medical Center. It represents a secondary analysis of a prospective cohort study of critically ill and injured adults. The primary purpose was to determine the role of sex and sex hormones on outcomes in critically ill and injured patients. The methods have been detailed previously [15]. Briefly, patients 18 years of age or older, admitted to the Surgical or Trauma Intensive Care Units (ICUs) of Vanderbilt University Medical Center or the University of Virginia Health Systems for at least 48 h were eligible for enrollment. Patients who died before 48 h were excluded, as were patients discharged from the ICU prior to 48 h. The minimum stay of 48 h was intended to exclude postoperative surgical patients with short observational stays as well as patients who died early from illness beyond the aid of modern critical care. This criterion selected a patient population at high risk for nosocomial infections, thus increasing power while limiting the required sample size. Patient care was at the discretion of the attending physician according to established critical care protocols in the respective ICUs.

Measure of obesity

Body mass index (BMI) was determined at hospital admission by dividing the weight in kilograms by the height in meters squared. Patients were classified into the following BMI groups according to the National Heart, Lung and Blood Institute guidelines [16]: ≤ 18.5 kg/m² (underweight), 18.5–24.9 kg/m² (normal), 25–29.9 kg/m² (overweight), 30.0–39.9 kg/m² (obese), and ≥ 40.0 kg/m² (severely obese). Patients with missing BMI data were excluded from the analysis.

Outcome measures

Infections were classified according to the definitions of the U.S. Centers for Disease Control and Prevention (CDC). Pulmonary infection was diagnosed when a predominant organism was isolated from an appropriately obtained culture in the setting of purulent sputum production, a new or changing infiltrate on chest radiography, and systemic evidence of infection. Quantitative endotracheal suction was used routinely at the University of Virginia ($> 10^5$ organisms/mL considered positive), and quantitative bronchoalveolar lavage was used routinely at Vanderbilt University ($> 10^4$ organisms/mL considered positive). Blood stream infections (BSIs) were diagnosed by the isolation of organisms from a blood culture from any site, with the exception of *Staphylococcus epidermidis* or other coagulase-negative staphylococci, which required isolation from two sites to be considered evidence of infection. Criteria for urinary tract infection included isolation of $> 10^5$ organisms/mL of urine or $> 10^4$ organisms/mL with dysuria. The criteria for

catheter-related infection included isolation of 15 or more colony-forming units from catheter tips by the semiquantitative roll plate technique in the setting of suspected infection (systemic symptoms or localized purulence). Incisional infections were diagnosed clinically, frequently without obtaining cultures.

Statistical analysis

Normally distributed continuous variables were summarized by means and standard deviations, and non-normal continuous variables were summarized as medians and interquartile ranges. For comparisons between multiple groups, one-way analysis of variance (ANOVA) was used with Bonferroni correction for multiple comparisons. To estimate the relation between infection outcomes (infection as a dichotomous variable) and BMI group, multivariate logistic regression was used to determine adjusted odds ratios (ORs). To determine the relation between infection incidence and BMI group, infection incidence rates were calculated per 1,000 ICU days. Multivariate Poisson regression using ICU days as the exposure variable was used to estimate the adjusted incidence rate ratios for site-specific infections. Only infectious sites with at least 50 events were included in the multivariable analysis.

Stata version 9.2 (Stata Corp., College Station, Texas, USA) was used for analysis. Tests for statistical significance were two-sided with an alpha of 0.05. All data are maintained in a secure, password-protected database that is compliant with the Health Insurance Portability and Accountability Act. All patient information was de-identified prior to analysis and reporting.

Results

Demographic and clinical characteristics of study population

A total of 2,291 patients were enrolled in the original study. Two hundred fifty-four patients (11%) were excluded from this analysis because of missing BMI data. The demographics and clinical characteristics of the remaining 2,037 patients are summarized in Table 1. The majority of patients fell into the normal (33%) and overweight (30%) categories, but the prevalence of obesity (24%) and severe obesity (9%) was high. Few patients were classified as underweight (3%). Patients in the normal weight group were younger (47 ± 20 years) than patients in both the overweight (50 ± 19 years; $p = 0.04$) and obese (52 ± 17 years; $p = 0.001$) groups. Patients in both the underweight and the severely obese groups were statistically more likely to be female than patients in the normal, overweight, and obese categories ($p < 0.01$ for all comparisons), whereas the sex distribution between these latter groups was not different. This distribution was similar to the proportion of patients who were trauma victims. Patients in both the underweight and the severely obese group were statistically less likely to be victims of trauma than patients in the normal, overweight, and obese categories ($p < 0.01$ for all comparisons), whereas the distribution between trauma and non-trauma patients did not differ in these latter groups. Groups were not different according to race.

There was no difference between groups in illness severity as measured by the Acute Physiology and Chronic Health

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS BY BODY MASS INDEX^a

	<i>Underweight</i> (n = 640)	<i>Normal weight</i> (n = 672)	<i>Overweight</i> (n = 615)	<i>Obese</i> (n = 494)	<i>Severely obese</i> (n = 192)	P value
Age (years)	53 ± 20	47 ± 20	50 ± 19	52 ± 17	49 ± 15	<0.001
Percent male	45	66	73	65	45	<0.001
BMI	18	23	27	33	45	<0.001
Percent trauma victims	36	63	66	58	42	<0.001
Race (%)						
White, non-Hispanic	77	83	83	83	86	NS
Black	19	10	13	12	10	NS
Other	4	7	4	5	4	NS
APACHE II score	17 ± 7	18 ± 6	17 ± 6	18 ± 6	16 ± 5	NS
ISS	29	34	30	33	27	0.006
TRISS (predicted survival)	0.83	0.69	0.73	0.72	0.82	0.004
Pre-ICU admission co-morbidity (%)						
Diabetes mellitus	14	9	15	22	37	<0.001
Cardiac disease	28	17	21	22	29	<0.001
Cerebrovascular disease	10	5	5	5	4	NS
Pulmonary disease	3	2	2	2	7	<0.001
Chronic renal insufficiency	19	5	4	4	7	<0.001
Dialysis dependence	8	3	2	1	2	0.02
HIV/AIDS	2	0	0	0	0	NS
Malignant disease	22	12	11	14	5	0.002
Hepatic insufficiency	3	4	6	6	3	NS
Hyperlipidemia	8	3	4	8	12	<0.001
Hypertension	36	24	30	38	48	<0.001
Peripheral vascular disease	6	6	6	3	6	NS
Rheumatic/connective tissue disorder	3	2	2	2	3	NS
Thyroid disease	5	5	4	5	8	NS
Chronic corticosteroid use	8	3	3	6	4	0.02
Inflammatory bowel disease	8	2	1	2	2	0.007
Death (%)	22	16	16	15	13	NS
ICU length of stay (days)	9.5	9	9	11	12	0.002

^aComparisons made using one-way analysis of variance (ANOVA). P value represents composite ANOVA.

BMI = body mass index; NS = not significant; APACHE = Acute Physiology and Chronic Health; ISS = Injury Severity Score; TRISS = Trauma-Related Injury Severity Score; ICU = intensive care unit; HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome.

Evaluation (APACHE) II score. For trauma patients, severely obese patients had a lower injury severity than normal weight patients (median Injury Severity Score [ISS] 27 vs. 34; $p = 0.008$), and normal weight patients had a statistically lower predicted survival than overweight patients (median Trauma-Related Injury Severity Score [TRISS] 0.69 vs. 0.73; $p = 0.04$). Although the predicted survival of the obese (0.72) and severely obese (0.82) patients also was higher than that of the normal weight group (0.69), these differences did not reach statistical significance ($p = 0.09$ and $p = 0.06$, respectively). Underweight patients were more likely to suffer from cerebrovascular disease, chronic renal insufficiency, dialysis dependence, malignant disease, and inflammatory bowel disease, whereas severely obese patients were more likely to suffer from diabetes mellitus, cardiac disease, hyperlipidemia, and hypertension.

The overall 28-day mortality rate was 16% (316 deaths). The mortality rate did not differ between BMI groups in the univariable analysis ($p = 0.40$) or multivariable analysis adjusting for age, sex, trauma status, and illness severity. Despite the absence of a difference in the mortality rate by BMI group, both obese and severely obese patients had longer ICU stays than normal weight patients. The severity-adjusted increase in ICU length of stay was 2.8 days (CI 0.47, 5.1; $p < 0.01$) for obese patients and 5.7 days (CI 2.5, 8.8) for severely obese patients.

Infection outcomes

There were 1,436 infection episodes involving 1,538 sites (1.1 sites/episode; some events involved more than one site) in 966 patients (47%). Pneumonia was the most common in-

TABLE 2. PERCENT OF INFECTIONS BY SITE AND BODY MASS INDEX^a

Infection	Underweight (n = 64)	Normal weight (n = 672)	Overweight (n = 615)	Obese (n = 494)	Severely obese (n = 192)	P-value
Any	36	47	47	49	51	NS
Pneumonia	19	34	33	33	27	0.05
Blood stream	16	14	16	17	25	0.009
Urinary tract	11	9	11	11	15	NS
Catheter-related blood stream	8	6	7	11	16	<0.001
Incision	6	5	4	6	6	NS
Intra-abdominal	5	3	5	5	6	NS

^aComparisons made using one-way analysis of variance (ANOVA) with Bonferroni correction. P value represents composite ANOVA. NS = not significant.

fection (n = 658), followed by blood stream (n = 330), urinary tract (n = 220), catheter-related (n = 173), incisional (n = 97), and intra-abdominal (n = 93) infections. Other sites of infection included the central nervous system (n = 1), pleura (n = 25), skin and soft tissue (n = 13), upper gastrointestinal tract (n = 5), vagina (n = 10), and colon (n = 10).

The distribution of infection episodes by anatomic site stratified by BMI group is summarized in Table 2. There was no difference in the rate of "any nosocomial infection" by BMI group (p = 0.31). Differences in the rates of pneumonia by BMI group approached, but did not reach, statistical significance (p = 0.06). Blood stream infections were significantly more common in severely obese patients (25%) than in normal weight (14%; p = 0.003) and overweight (16%; p = 0.02) patients. Urinary tract infections were not different by BMI group (p = 0.26). Catheter-related infections were more common in severely obese patients (16%) than in either normal weight (6%; p < 0.001) or overweight (7%; p < 0.001) patients. Obese patients also were more likely to have catheter-related infections (11%) than were normal weight patients (p = 0.03).

Table 3 summarizes the age-, sex-, and severity-adjusted odds ratios for site-specific infections by BMI group. Severely obese patients were more likely to suffer blood stream (OR 2.2; 95% CI 1.5, 3.4) and catheter-related (OR 3.2; 95% CI 1.9, 5.3) infections than were normal weight patients. Obese patients were also at higher risk for catheter-related infections

(OR 1.9; 95% CI 1.2, 2.9). These results remained after stratification for trauma status. Other sites of infection did not demonstrate BMI group-dependent patterns.

Table 4 summarizes the site-specific infection incidence rates per 1,000 ICU days by BMI group, and Table 5 summarizes the adjusted incidence rate ratios (IRRs) by BMI group with the normal weight group serving as the reference. Catheter-related infections remained statistically more frequent in severely obese patients (IRR 1.9; 95% CI 1.2, 3.0). Although the previous trends were replicated, other changes did not reach statistical significance. Normal weight patients were at significantly higher risk for pneumonia, but this observation was explained by the higher rate of severe head injury in this group. After adjusting for head injury scores, the difference in pneumonia rates between normal and severely obese patients was no longer statistically significant (IRR 0.71; 95% CI 0.45, 1.11).

Table 5 summarizes microbiology data from available cultures by BMI group. There was no difference in broad categories of organisms (gram-positive vs. gram-negative, etc.) by BMI group, nor was there a difference in the prevalence of organisms commonly responsible for blood stream and catheter-related infections. *Clostridium difficile* colitis accounted for only 29 infection episodes and therefore was not included in the multivariable analysis. There was no difference in *C. difficile* infections by BMI group in the univariable analysis (p = 0.69).

TABLE 3. ODDS RATIO RELATIVE TO NORMAL WEIGHT PATIENTS ADJUSTED FOR AGE, SEX, AND ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II SCORE (95% CONFIDENCE INTERVAL) BY INFECTION SITE AND BODY MASS INDEX FOR SITES WITH MINIMUM OF 50 EVENTS^{a,b}

Infection	Underweight (n = 64)	Overweight (n = 672)	Obese (n = 495)	Severely obese (n = 192)
Any site	0.69 (0.40, 1.20)	1.10 (0.85, 1.30)	1.10 (0.88, 1.40)	1.30 (0.91, 1.80)
Pneumonia	0.52 (0.27, 1.10)	0.97 (0.77, 1.20)	1.00 (0.92, 1.30)	0.79 (0.55, 1.10)
Blood stream	1.30 (0.62, 2.50)	1.10 (0.84, 1.60)	1.20 (0.90, 1.70)	2.20 (1.50, 3.4)^c
Urinary tract	0.93 (0.40, 2.10)	1.30 (0.86, 1.80)	1.20 (0.81, 1.80)	1.40 (0.89, 2.30)
Catheter-related blood stream	1.30 (0.48, 3.40)	1.30 (0.81, 2.00)	1.90 (1.20, 2.90)	3.20 (1.90, 5.30)
Incision	1.80 (0.56, 5.60)	0.69 (0.39, 1.20)	1.10 (0.66, 1.90)	1.10 (0.54, 2.40)
Intra-abdominal	1.20 (0.60, 2.50)	1.20 (0.69, 1.90)	0.73 (0.41, 1.30)	1.30 (0.44, 3.80)

^aSome infection episodes involved more than one site.

^bNormal weight set as 1.00.

^cBoldface type indicates statistically significant difference.

TABLE 4. SITE-SPECIFIC INFECTION INCIDENCE BY BODY MASS INDEX/1,000 INTENSIVE CARE UNIT DAYS

<i>Infection</i>	<i>Underweight (n = 64)</i>	<i>Normal weight (n = 672)</i>	<i>Overweight (n = 615)</i>	<i>Obese (n = 494)</i>	<i>Severely obese (n = 192)</i>
Pneumonia	14.6	27.9	26.4	22.1	14.9
Blood stream	12.1	11.6	12.4	11.1	14.0
Urinary tract	8.5	7.8	8.5	7.6	8.5
Catheter-related blood stream	6.0	4.8	5.7	7.2	9.3
Incision	4.8	3.9	2.9	3.7	3.2
Intra-abdominal	3.6	2.4	3.7	3.9	3.5

Discussion

Conventional wisdom suggests that obesity increases the risk of adverse outcomes during critical illness, but an independent effect of obesity on outcomes has never been demonstrated conclusively in the ICU setting. Early reports suggested that obesity played a large role in determining outcomes in the ICU and after trauma [5–7], but more recent reports have suggested no relation [9,10,12,13]. Conclusions from the published literature are limited by the fact that these have been mostly retrospective studies with differing definitions and various incidences of obesity. We sought to describe the relation of obesity to site-specific ICU-acquired infections in a large, prospective population of surgical and trauma patients with a prevalence of obesity reflecting that in the general population. We hypothesized that obese patients would be at higher risk for ICU-acquired infections at all sites.

To our knowledge, these are among the first data to demonstrate obesity to be an independent risk factor for blood stream and catheter-related infections in the ICU. The mechanisms accounting for this observation are unclear, but a potential explanation relates to the difficulty in achieving vascular access—both peripheral and central—in obese patients. Placement of central catheters is more difficult because of the loss of physical landmarks [17] and the longer distance from superficial structures to central veins [18]. Modifications in standard techniques have been described, including the use of spinal needles [19] or ultrasound guidance [20], but provider experience with these modifications is variable. Although it has never been demonstrated conclusively, pro-

viders may hesitate to discontinue central venous catheters in obese patients, even in the setting of signs or symptoms of infection. Another possible explanation is that obese and severely obese patients require longer severity-adjusted ICU stays, therefore increasing their risk of nosocomial infections. All of the nosocomial infections were associated with longer age-, sex-, and severity-adjusted ICU stays (from 8–12 days longer depending on the infection), but whether nosocomial infections were the cause or the result of longer ICU stays is unclear.

In contrast to other investigators [6], we did not detect a difference in pneumonia rates by BMI group. Obese and severely obese patients have multiple risk factors for pulmonary complications, but our data suggest that their risk for ICU-acquired pneumonia is no higher than that in normal weight patients. These risk factors may be offset by ventilator and infection-control strategies that minimize ICU-acquired and ventilator-associated pneumonia. We also did not detect a difference in the mortality rate related to BMI. As the prevalence of obesity has increased, hospitals and providers have become more accustomed to caring for this special needs patient group, and these findings may reflect this difference. Hospitals are more likely to have equipment such as specialty beds and larger radiology and physical therapy equipment. In addition, improved management of associated chronic morbidities in the outpatient setting (the aggressive use of anti-platelet agents, lipid agents, and strict glucose control) may reduce the extra morbidity and mortality historically attributed to obesity.

The strengths of this study include its large size and prospective nature and its enrollment of patients from two

TABLE 5. INCIDENCE RATE RATIO RELATIVE TO NORMAL WEIGHT PATIENTS ADJUSTED FOR AGE, SEX, AND ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II SCORE (95% CONFIDENCE INTERVAL) BY INFECTION SITE AND BODY MASS INDEX FOR SITES WITH MINIMUM OF 100 EVENTS^{a,b}

	<i>Underweight (n = 64)</i>	<i>Overweight (n = 672)</i>	<i>Obese (n = 495)</i>	<i>Severely obese (n = 192)</i>
Pneumonia	0.57 (0.32, 1.10)	0.93 (0.77, 1.10)	0.82 (0.67, 1.00)	0.58 (0.43, 0.79)^c
Blood stream	1.10 (0.59, 2.20)	1.10 (0.81, 1.40)	0.95 (0.70, 1.30)	1.20 (0.90, 1.80)
Urinary tract	0.98 (0.45, 2.10)	1.20 (0.87, 1.80)	0.93 (0.65, 1.30)	0.94 (0.60, 1.50)
Catheter-related blood stream	1.20 (0.48, 3.10)	1.20 (0.79, 1.90)	1.50 (0.96, 2.20)	1.90 (1.20, 3.00)
Incision	1.40 (0.49, 3.90)	0.68 (0.39, 1.20)	0.94 (0.57, 1.60)	0.68 (0.34, 1.30)
Intra-abdominal	1.50 (0.44, 4.90)	1.60 (0.90, 2.80)	1.50 (0.87, 2.70)	1.40 (0.68, 2.90)

^aSome infection episodes involved more than one site.

^bNormal weight set as 1.00.

^cBoldface type indicates statistically significant difference.

institutions and three distinct intensive care units. Despite these strengths, there are several important limitations. First, although BMI correlates with chronic disease, its use as a surrogate for obesity in the critical care setting has been criticized because rapid fluctuations in volume status may alter weight measurements. Despite these criticisms, alternatives are limited, and BMI is highly correlated with more complicated measures of obesity (waist circumference, electrical impedance) [21,22]. To minimize this bias, weight was measured immediately on hospital admission. A second limitation of this study is that patients remaining in the ICU less than 48 h (died or were discharged) were excluded, introducing the possibility that these results cannot be generalized to all ICU patients. As this inclusion criterion was chosen to identify a patient population at high risk for nosocomial infections, we believe the results can be applied appropriately to patients with ICU stays greater than 48 h. Finally, we did not collect information on the number of catheter days, which clearly influences the rate of catheter-related infections. It is possible (indeed probable) that obese patients had more severity-adjusted catheter days than normal weight patients.

Conclusion

Obesity is an independent risk factor for catheter-related and blood stream infections, possibly because of the difficulty in obtaining venous access in these patients and the reluctance of providers to discontinue established venous catheters in the setting of infection signs and symptoms.

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Author Disclosure Statement

The authors have no conflicts of interest to disclose.

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