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Obesity in critically ill patients is associated with increased need of mechanical ventilation but not with mortality

Sascha Tafelski[a], **Hailong Yi**[a], **Fakher Ismaeel**[b], **Alexander Krannich**[c], **Claudia Spies**[a], **Irit Nachtigall**[a,*]

[a] *Department of Anaesthesiology and Intensive Care, Charité — Universitaetsmedizin Berlin, Campus Charité Mitte and Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany*
[b] *Department of Gynaecology, Campus Virchow Clinic, Charité Medical University Berlin, Augustenburger Platz 1, Berlin 13353, Germany*
[c] *Department of Biostatistics, Clinical Research Unit, Berlin Institute of Health, Charité — University Medicine Berlin, Berlin, Germany*

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Summary Worldwide incidence of obesity is increasing and impaired outcome in postoperative patients has been described. Antibiotic prescribing is complicated by different pharmacology in this population. This study evaluates mortality and morbidity of obese postoperative patients and explores possible relation to antibiotic therapy. Therefore, data obtained in a prospective study in 2009—2010 were analysed. Postoperative patients on 5 ICUs were included with >48 h of ICU treatment and documented body-mass-index (BMI). Altogether 451 non-obese patients (BMI < 30 kg/m^2) were compared with 130 obese patients including propensity score matching. There was significant heterogeneity of baseline characteristics. ICU-mortality was 7.5% in non-obese and 7.7% in obese patients ($p > 0.999$), but 65.4% of obese patients required mechanical ventilation compared with only 53.2% of non-obese patients ($p = 0.016$). These findings were validated in multivariate regression analyses (adjusted OR for ICU-mortality for obese patients 0.53, 95%-CI 0.188—1.321, $p = 0.197$; adjusted OR for mechanical ventilation 1.841, 95%-CI 1.113—3.076, $p = 0.018$). Results were confirmed by propensity score matching. Therapeutic drug monitoring for vancomycin (TDM) showed that underdosing and overdosing occurred more often in obese patients and sufficient TDM levels were

* Corresponding author. Tel.: +49 30 450 551102; fax: +49 30 450 551900.
E-mail address: irit.nachtigall@charite.de (I. Nachtigall).

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less often achieved. In conclusion, obesity is associated with increased morbidity but ICU mortality is equal compared with a non-obese population. Pharmacological differences might explain observed differences in antibiotic therapy and in obese patients TDM might be especially of importance.

Introduction

In the intensive care unit (ICU) obesity is a common comorbidity in about 20% of patients and rising incidence is described worldwide [1]. In concordance with the World Health Organisation, obesity is most commonly defined as a body mass index (BMI) of $\geq$30 kg/m^2 [2,3]. Obesity is associated with increased morbidity of ICU patients but there remains uncertainty regarding the effect on mortality. Similar mortality rates were described by several authors comparing obese and non-obese ICU patients [4,5]. These findings were contrasted by a meta-analysis of Fezeu et al. [6] that described a significantly higher mortality in obese ICU patients with H1N1 influenza for death. A doubled mortality rate was also found in obese medical ICU patients admitted due to obstructive airway disease, pneumonia, and sepsis [7]. Similarly, in a cohort study of patients following trauma Byrnes et al. described an increased mortality rate for obese patients [8]. However, other authors described even lower mortality in obese patients [9]. Potential mechanisms to explain this variance are still under debate. There is evidence that obese patients experience higher postoperative pain intensity and are under higher risk to acquire postoperative infections [10—12]. Nosocomial infections and especially pneumonia and surgical site infections were found to occur more often in obese patients [13,14]. A recent study by Ferrada et al. focussing on patients following emergency surgery described higher rates for surgical site infections [15]. Other authors reported that weight-adapted dosing strategies for benzodiazepines and opioids were one factor altering outcome [16]. In this context, differences in pharmacokinetics and pharmacodynamics in obese patients were described for volume of distribution, changes in hepatic metabolism and renal function that may lead to antibiotic overdosing as well as underdosing [17,18]. Currently, there is a lack of evidence to guide an optimal dosing regimen for antibiotic agents [18]. Antibiotic dosing is most commonly based on weight together with renal or hepatic function and can be adapted using results from therapeutic drug monitoring for some agents [19]. In summary, obese patients seem to experience increased morbidity following surgery but relation on overall outcome is not completely clear. Furthermore, there is currently no conclusive mechanism identified that might explain a potential protective effect on outcome [20]. Attention has been drawn to dosing of antiinfective agents in obese ICU patients as one potential contributing factor [18,21]. Against this background, we conducted this observational study in postoperative ICU patients. The aims of this study were to assess ICU mortality in obese patients and to compare outcome with non-obese patients; to describe perioperative morbidity and to relate outcome with antibiotic therapy including therapeutic drug monitoring.

Material and methods

Study design and setting

This study was conducted as secondary analysis of a prospective interventional study [22]. This initial trial was performed at Charité hospital, a tertiary university hospital in Berlin, Germany. The study evaluates an ICU stewardship program of the ABx Study Group (ISRCTN54598675) on infection management and included all consecutively admitted ICU patients [22]. Data used for the present analysis were obtained from August 2009 to April 2010 including patients predominantly following surgery or major trauma. The study wards comprised five surgical ICUs with a focus on postoperative patients from different surgical disciplines (neurosurgery, abdominal surgery, cardiac surgery, trauma, gynaecology) and patients with major trauma. The project was approved by the local Ethics Review Board and the data safety authorities. The Ethics Review Board waived the need for informed consent.

Patients and data collection

Patients older than 18 years admitted to one of the ICUs with at least two days of ICU

treatment were included into this study. For analysis, patients were excluded when anthropometric values of weight and body height were not documented to calculate body mass index (BMI). All data were prospectively obtained during ICU stay.

Definitions and measurement

Obesity classification was applied based on the calculated BMI with a range of $\geq 30\,kg/m^2$ for obese patients and $<30\,kg/m^2$ representing the non-obese control population.

The primary outcome parameter was all cause ICU mortality. Secondary, postoperative morbidity of patients was focussed defined as requirement of invasive mechanical ventilation via any endotracheal tube; as was diagnosis of infections on ICU admission or during ICU stay. Furthermore, the trial incorporated assessment of quality of antibiotic therapy. Therefore, antibiotic treatment and infection diagnostics were reviewed by infectiological experts for every ICU day of every patient. Indication of antibiotic therapy was evaluated as well as chosen agents or combination therapy as described previously [22]. Briefly, for all ICU days every application of an antibiotic agent was assessed. It was evaluated, whether the antibiotic was prescribed with sufficient evidence for an infection and whether applied drugs were recommended by the hospital antibiotic guideline for this indication. Subsequently, reassessment of antibiotic therapy was evaluated. De-escalation of therapy is recommended in case of resolution of clinical signs of infection to avoid unnecessary prolonged antibiotic exposure. Every ICU day in concordance with guidelines was divided by all observed ICU days and transferred into a relative measurement [22]. Exemplarily, for vancomycin therapy an initial loading dose of 1 g intravenous drug is recommended independent from renal function. This loading dose is then followed by continuous infusion or followed by intermittent administration. For continuous vancomycin infusion in patients with normal renal function, 2 g vancomycin is applied during 24 h using a central line; for intermittent administration 500 mg vancomycin is given every 6 h or 1 g vancomycin is given every 12 h with duration of infusion of at least 1 h. Therapeutic drug monitoring (TDM) is advised to be initiated after 24 h of continuous vancomycin administration or just before the 4th administration of intermittent vancomycin infusion. This dosing protocol has been implemented in the study wards and is available as a national stewardship program (www.dgai-abx.de). Vancomycin is an agent that is frequently applied in our ICU population and therapeutic drug monitoring (TDM) is established in clinical routine, we were able to include analyse of antibiotic serum levels into this study. For this purpose, the subgroup of patients with vancomycin therapy during ICU treatment was further explored. In these patients vancomycin serum trough levels were evaluated. Although optimal vancomycin serum levels are under debate in the ICU setting, our hospital policy included recommendations to achieve and maintain a serum level of 10—20 mg/L vancomycin. Consequently, serum levels of less than 10 mg/L vancomycin were classified as underdosed and were expected to be the threshold for dosing changes with an increase of daily vancomycin dosage. Serum levels of more than 20 mg/L vancomycin were classified as overdosed and vancomycin therapy had to be adapted [23]. To further quantify underdosing and overdosing, percentage of all days with TDM results above and below targeted trough serum levels of 10—20 mg/L vancomycin were calculated for each patient.

Statistical analysis and ethic review

Results are given depending on their scale in proportions (%), median including 25—75% quartiles (25|75) or arithmetic mean and standard deviation (mean ± STD). As appropriate, tests for statistical significance were performed with two-tailed Student's *t*-test, Wilcoxon—Mann—Whitney test or Fisher's exact test. A *p*-value <0.05 was considered to be statistically significant. Multivariate analyses of binary outcome parameters were realised by logistic regression and visualized by showing related odds ratios with 95% confidence intervals. For logistic regression analysis, all covariables entered the model (age, female sex, SAPS II on admission, pre-existing comorbidities, surgery, Infections on ICU and BMI group) and were processed in a backward selected model with all cause ICU mortality or requirement of invasive mechanical ventilation as dependent variable. These results were backed up using the method of Propensity score matching as described in [24]. Therefore, patients were matched according to BMI status using the selected variables in the logistic regression models to account for heterogeneity of all relevant baseline characteristics. The resulting propensity scores for patients were used for 1:1 nearest neighbour matching and achieved balanced groups in regard to baseline characteristics except for the factor of obesity. All analyses were performed with IBM SPSS 22.0 and R 3.0.2.

Table 1 Patients characteristics.

Variable	Non-obese $N = 451$	Obese patients $N = 130$	p-Value
BMI median (25%|75% quartiles)	25 (23|27)	34 (31|37)	<0.001
Age median (25%|75% quartiles)	63 (50|72)	64 (53|72)	0.346
Female sex *N* (%)	193 (43%)	61 (47%)	0.404
SAPS II median (25%|75% quartiles)	36 (24|48)	35 (25|53)	0.351
Pre-existing comorbidities *N* (%)			
Immune suppression	35 (8%)	10 (8%)	>0.999
Cardiac	236 (52%)	90 (69%)	0.001
Vascular	183 (41%)	67 (52%)	0.027
Pulmonary	103 (23%)	24 (19%)	0.336
Hepatic	48 (11%)	23 (18%)	0.034
Renal	101 (22%)	47 (36%)	0.002
Diabetes mellitus	155 (34%)	85 (65%)	<0.001
Neurological	109 (24%)	31 (24%)	>0.999
Immunological	17 (3.8%)	6 (4.6%)	0.616
Oncological	122 (27%)	34 (26%)	0.911
Surgical admission	327 (73%)	100 (77%)	0.367
OP — category *N* (%)			
Head/neck/extracranial	22 (5%)	6 (5%)	>0.999
Abdomen	88 (20%)	26 (20%)	0.901
Intracranial	70 (16%)	9 (7%)	0.013
Musculoscelettal	40 (9%)	11 (9%)	>0.999
Vascular	5 (1%)	0 (0%)	0.592
Cardial	92 (20%)	43 (33%)	0.003
Pulmonary	4 (1%)	1 (1%)	>0.999
Urogenital	3 (1%)	1 (1%)	>0.999
Trauma	3 (1%)	3 (1%)	>0.999

Results

Patients baseline characteristics

Altogether 696 consecutive ICU patients were primarily screened for study inclusion. Finally, 581 patients fulfilled inclusion criteria and had anthropometric parameters documented, 451 with a BMI $< 30\,kg/m^2$ and 130 with a BMI $\geq 30\,kg/m^2$. Obese patients presented significantly more often with pre-existing diabetes mellitus and sequelae of metabolic syndrome like cardiac or renal comorbidity. Consequently, admissions following cardio-surgical procedures were more common in this group (Table 1).

Hospital mortality and morbidity

The all cause ICU mortality in the population was 44 out of 581 patients (7.6%) and distributed equally between study groups, as was length of ICU stay. Obese patients required significantly more often invasive ventilation. In the subgroup of patients with invasive ventilation, duration of mechanical ventilator support was comparable (Table 2). Occurrence of infections was also distributed equally between groups and especially pneumonia and infections of soft tissues did not show significant differences between obese and non-obese patients.

Antibiotic therapy

Quality of antibiotic therapy did not differ significantly in terms of overall adherence to locally adapted guidelines. In non-obese patients mean $74 \pm 32\%$ ICU days were found concordant with guidelines compared with $76 \pm 32\%$ in obese patient ($p = 0.488$).

Vancomycin therapy was applied in a subgroup of 117 patients, 91 non-obese patients versus 26 obese patients (Table 3). Evaluating all therapy days, mean serum levels did not differ between obese and non-obese patients. Further exploration of vancomycin TDM results in this subgroup revealed that overdosing and underdosing occurred more often in obese patients without reaching statistical significance level. Notably, when evaluating the first trough TDM level measured, significantly less

Table 2 Mortality, morbidity and infections of patients during ICU stay.

Variable	Non-obese $N = 451$	Obese patients $N = 130$	p-Value
Mortality N (%)	34 (7.5%)	10 (7.7%)	>0.999
ICU stay in days; median (25|75%)	6 (4|14)	6 (4|12)	0.833
Mechanical ventilation N (%)	240 (53.2%)	85 (65.4%)	0.016
Duration of ventilation in days[a] median (25|75%)	3 (1|14)	3 (1|10)	0.374
Infections on ICU in N (%)			
Pneumonia	153 (34%)	39 (30%)	0.459
Abdominal	43 (10%)	10 (8%)	0.606
Urinary	25 (6%)	8 (6%)	0.830
Bones and joints	13 (3%)	5 (5%)	0.569
Endocarditis	12 (3%)	3 (2%)	>0.999
Soft tissue	21 (5%)	4 (3%)	0.624
Bacteraemia	28 (6%)	14 (11%)	0.085
Infection with unknown focus	17 (4%)	11 (9%)	0.036
Number patients with >1 infections	59 (13.1%)	22 (16.9%)	0.314

[a] For evaluation of duration of ventilation only patients with mechanical ventilator support were included.

obese patients achieved a targeted serum level of 10—20 mg/dl and consequently therapy had to be adapted (Table 3).

Multivariate analysis for ICU mortality and morbidity

All cause ICU mortality was evaluated as dependent variable in multivariate logistic regression analyses to account for differences in patient characteristics between study groups. All variables entered the regression model and were processed in a backward elimination procedure. After exclusion of non-significant and non-explaining variables, the resulting multivariable regression analysis showed that obese patients had a non-significantly reduced risk for ICU mortality compared with non-obese patients (adjusted OR 0.53, 95%-CI 0.188—1.321, $p = 0.197$) as displayed in Fig. 1.

This procedure was repeated for morbidity analysing requirement of mechanical ventilation. The resulting model showed a significantly increased risk for obese patients for invasive ventilator support on ICU stay with an adjusted OR of 1.841 (95%-CI 1.113—3.076, $p = 0.018$, see Fig. 2).

In a confirmatory analysis using the technique of propensity score matching, the cohort was re-evaluated. The resulting 1:1 matched population included 260 patients. In 130 obese patients altogether 10 cases died compared with 11 cases out of 130 non-obese patients (7.7% versus 8.5%, $p = 0.902$). Morbidity differed significantly between groups in the matched population with 85 out of 130 (65.4%) obese patients requiring mechanical ventilation compared with 63 out of 130 (48.5%) non-obese patients ($p = 0.008$). Duration of mechanical ventilation was as well not different between matched study groups [median 3 days (1|9) obese versus 3 (1|12) non-obese patients, $p = 0.591$] in this analysis paralleling the findings of the univariate analysis.

Table 3 Subgroup of patients with vancomycin therapy and results of therapeutic drug monitoring for obese and non-obese patients (mean ± SD).

Variable	Non-obese $N = 91$	Obese patients $N = 26$	p-Value
Mean vancomycin trough levels in mg/L	16.6 ± 7.8	18.2 ± 8.0	0.303
Fraction of vancomycin trough levels below 10 mg/L (% of measurements)	22 ± 32	27 ± 35	0.507
Fraction of vancomycin trough levels above 20 mg/L (% of measurements)	27 ± 33	39 ± 38	0.169
Achievement of reference vancomycin trough level (10—20 mg/L) in first TDM, N patients (%)	43 (47%)	6 (23%)	0.041

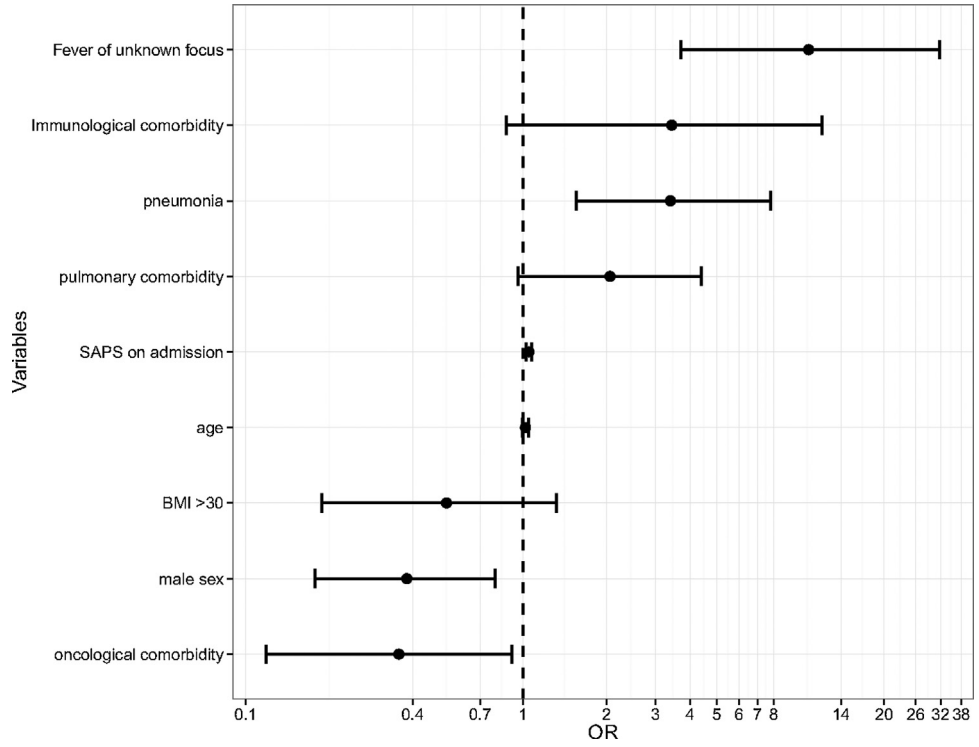

Figure 1 Results of the multivariable regression analysis evaluating all cause ICU mortality for obese compared with non-obese patients. OR and confidence intervals are displayed.

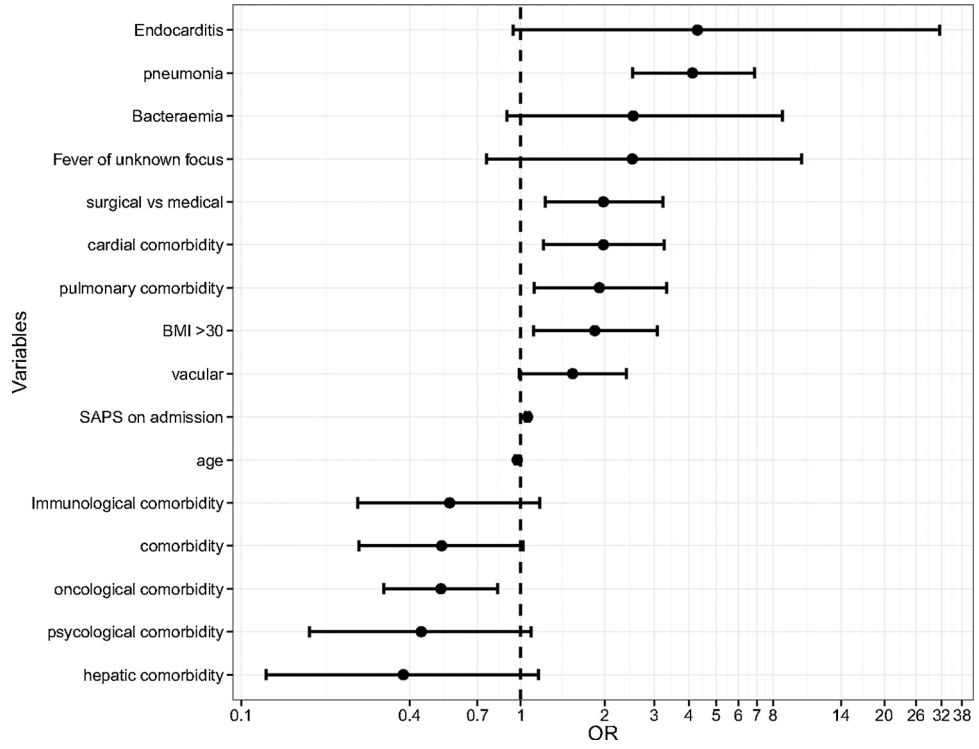

Figure 2 Results of the multivariable regression analysis evaluating all requirements of mechanical ventilation for obese compared with non-obese patients. OR and confidence intervals are displayed.

Discussion

The most important finding of this study was that we did not find a difference between obese and non-obese patients regarding ICU mortality. Distribution of infections was similar but significantly more obese patients required mechanical ventilation. Obese patients presented more frequently with relevant comorbidities. In addition, quality of antibiotic therapy was similar between groups but differences in vancomycin serum levels suggest that dosing is more complicated in obese ICU patients.

After evaluation of baseline characteristics, anticipated differences between non-obese and obese patients were observed. Obese patients presented significantly more often with comorbidities corresponding to the trial of the metabolic syndrome with cardiovascular diseases like arterial hypertension or heart insufficiency and diabetes mellitus [25]. Consequently, operative admission diagnoses were different with more obese patients being admitted to ICU following cardiac surgery.

In our dataset, we identified a higher frequency of postoperative mechanical ventilation in obese patients, a circumstance that has been described previously [26,27]. Ventilator support has been identified as one major risk factor for development of pneumonia in the ICU setting [28] and pneumonia itself inherits an attributable mortality of about 10% due to this complication [29]. Based on this, it could be expected that more obese patients are observed with fatal outcome in our study. In contrast, in our study obese patients were found to have similar mortality compared with non-obese patients. This phenomenon has already been described as obesity paradox [9]. As all-cause ICU mortality is influenced by multiple factors or imbalances in baseline characteristics we carefully evaluated our data set to address heterogeneity between groups. Accordingly, we were able to perform a propensity score based matching procedure to optimize homogeneity of the resulting subpopulation concerning baseline characteristics. This technique was used to validate the multivariate logistic regression analyses and finally, no difference between obese and non-obese patients was found in regard to ICU mortality but in morbidity. However, it should be noted that due to the design of this study especially unobserved factors may interact with these results. As examples, patients exposure to antibiotics outside the observed ICU period or physical state of patients reflected in ASA status on admission may interact with results.

Additionally, we scrutinized quality of antibiotic therapy in the study population. Antiinfective management was found similar between groups when analysing choice, timing and duration of therapy and appropriate infection diagnostic. In contrast, obese patients where at higher risk for insufficient antibiotic dosing as we could observe significantly less obese patients with sufficient serum levels of vancomycin especially after induction of therapy. This finding is in concordance with the working group of Thursky et al. [21]. They recently reviewed relevant pharmacological differences between obese and non-obese patients and found that there might be evidence that a higher volume of distribution and relatively higher renal excretion could lead to altered serum levels of antibiotics. When exemplarily assessing vancomycin serum levels in our population, indeed we were able to identify differences in initial therapeutic drug levels. In obese patients serum trough levels after initiation of vancomycin therapy were more often out of targeted range and had to be adapted. In this context there arises the question whether dosing for other important antibiotics in critically ill patients are sufficient if they are not individually adapted to body weight [18,30]. Based on these findings dosing strategies used for non-obese patients should be transferred with caution to the obese population.

Limitations

This study evaluated prospectively obtained data and included a broad patient population in surgical ICUs. Principally, for this study design there is an inherent limitation to infer on causality in the non-randomized setting but we carefully evaluated relevant baseline characteristics for heterogeneity and used powerful statistical technique to account for imbalances. Yet, data analysis remains limited to observed variables and there are many further covariables that may be of interest to be explored. Exemplarily, this evaluation is limited to therapeutic drug monitoring performed regularly to achieve sufficient number of observations but analysis of other agents was not possible in this data set. Additionally, vancomycin is a hydrophilic antibiotic but results on this agent cannot simply be transferred to other antibiotics. Also, we were limited in regard to sufficient data evaluating hepatic or renal organ function and to data on ICU mortality as a longer follow up was not feasible in this trial.

Conclusion

Obese patients differ significantly from non-obese patients and they require more often mechanical

ventilation; however, mortality is similar between groups. Especially dosing of anti-infective agents like vancomycin seems to be more complicated in this population. When available, therapeutic drug monitoring may support optimizing therapy in obese patients and recommendations especially in the critical ill should tailor drug dosing also based on anthropometric parameters.

Conflicts of interest

This investigator initiated trial was designed, created and evaluated independently from funding and no sources of funding were used to prepare this article. Unrelated to this study, IN and ST have received lecture fees from Roche and Pfizer. CS or the institution received funding unrelated to this study from Grünenthal, Köhler Chemie, Roche, MSD SHARP & DOHME GmbH, Orion Pharma, Outcome Europe Sàrl, B. Braun Melsungen, AppAdventure, German Federation of Industrial Research Associations, Professional Association of German Anaesthesiologists, Federal Ministry of Education and Research, German Cancer Aid, German Aerospace Center, German Research Society, German Society for International Global Health Collaboration, Inner University Grants, Non-Profit Society Promoting Science and Education, European Commission Funding, European Society of Anaesthesiology, ConvaTec International Service GmbH, Pfizer Pharma, Vifor Pharma, Fresenius Kabi, and Georg Thieme Verlag.

Authors' contributions

ST, IN, and CS worked out the design and conception of the study. HY, AK and ST were responsible for data acquisition, analyses and interpretation. ST, HY, FI and AK revised the primary study data. ST and IN drafted the final manuscript to equal parts. FI, AK and CS revised the manuscript. All authors had full access to the data set and read and approved the final version of the manuscript.

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