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Methicillin-resistant *Staphylococcus aureus* bloodstream infections are associated with a higher energy deficit than other ICU-acquired bacteremia

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Take-home message: This study indicates that early negative energy balance is an independent determinant of methicillin-resistant *Staphylococcus aureus* nosocomial bacteremia in acute prolonged mechanically ventilated patients. Feeding prescriptions to limit early energy deficit during intensive care unit stay appear to be a potential way to optimize prevention of methicillin-resistant *S. aureus* nosocomial bacteremia.

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Abstract *Purpose:* Caloric insufficiency during the first week of intensive care unit (ICU) stay was reported to be associated with increased infection rates, especially ICU-acquired bloodstream infection (ICU-BSI). However, the predisposition to ICU-BSI by a given pathogen remains not well known. We aimed to determine the impact of early energy-calorie deficit on the pathogens responsible for ICU-BSI.
Design: Prospective, observational, cohort study in a 18-bed medical ICU of a tertiary care hospital.
Methods: Daily energy balance (energy-calorie intakes minus calculated energy-calorie expenditure) was compared according to the microbiological results of the blood cultures of 92 consecutive prolonged (at least 96 h) acute mechanically ventilated patients who developed a first episode of ICU-BSI. *Results:* Among the 92 ICU-BSI, nine were due to methicillin-resistant *Staphylococcus aureus* (MRSA). The cumulated energy deficit of patients with MRSA ICU-BSI was greater than those with ICU-BSI caused by other pathogens ($-1{,}348 \pm 260$ vs $-1{,}000 \pm 401$ kcal/day from ICU admission to day of ICU-BSI, $p = 0.008$). ICU admission, risk factors for nosocomial infections, nutritional status, and conditions potentially limiting feeding did not differ significantly between the two groups. Patients with MRSA ICU-BSI had lower delivered energy and similar energy expenditure, causing higher energy deficits. More severe energy deficit and higher rate of MRSA blood cultures ($p = 0.01$ comparing quartiles) were observed.
Conclusions: Early in-ICU energy deficit was associated with MRSA ICU-BSI in prolonged acute mechanically ventilated patients. Results suggest that limiting the early energy deficit could be a way to optimize MRSA ICU-BSI prevention.

Keywords Energy deficit · *Staphylococcus* · Critically ill patients · Nosocomial infection · Bacteremia

Introduction

Bacteremia is one of the major causes of nosocomial infection in the intensive care unit (ICU) [1–4]. ICU-acquired bloodstream infection (ICU-BSI) is associated with increased morbidity and length of stay, resulting in excess costs and high mortality of critically ill patients [3–7]. Although there are variations due to heterogeneous information sources and variety of local clinical practices, coagulase-negative staphylococci, *Staphylococcus aureus*,

and *Enterobacteriaceae* species are the pathogens most frequently responsible for nosocomial bacteremia [1, 3, 4, 6]. The distribution of pathogens responsible for nosocomial bacteremia differs markedly in the ICUs where multidrug-resistant bacteria like *Pseudomonas* spp. or methicillin-resistant staphylococci are highly dominant [2, 4, 8–10]. Increased mortality due to ICU-BSI is associated with host conditions, responsible pathogen(s), time to ICU-BSI, and appropriateness of treatment [4, 10]. Specialized ICUs, severity at ICU admission, longer length of ICU stay, colonization with multidrug-resistant pathogens, intravenous catheters or invasive procedures, and low caloric intake are known risk factors for developing ICU-BSI [3, 5–7, 10–12]. However, the predisposition to ICU-BSI by a given pathogen is still not well known, probably because the numerous risk factors for ICU-BSI may render the analysis of the susceptibility to infection by a given pathogen difficult.

Protein–energy malnutrition (PEM) is commonly associated with impaired immune responses and affects the clinical course of some infections, such as pneumonia or bacteremia [12–14]. ICU patients are prone to develop early protein–energy deficit. The latter is associated with a higher rate of nosocomial infections, longer ICU stays, and higher healthcare costs [15]. Energy deficit in ICU patients is mainly caused by reduced intake due to underprescribed calories and frequent feeding interruptions because of gastrointestinal intolerance or diagnostic and/or therapeutic procedures [16–19]. Energy deficit results in an early energy gap during the first week of ICU stay, which is never overcome thereafter [16]. Cumulated energy deficit build-up during the first days of ICU stay appears to be an independent factor contributing to nosocomial infections [15, 16, 20]. In addition, a large negative energy balance was observed during prolonged acute mechanical ventilation in the most critically ill patients and might affect their ICU outcomes [18]. However, randomized intervention studies limiting energy deficit by combining parenteral nutrition with insufficient enteral nutrition have yielded conflicting results among ICU-acquired nosocomial infections [21–23]. Indeed, limiting early energy deficit in ICU patients might be reserved for those that are in a situation of chronic critical illness, e.g., patients with prolonged acute mechanical ventilation (at least 96 h) and severe energy deficits are likely to benefit most from preventive measures [15, 24, 25]. In this context, we have previously shown that the level of energy deficit is an independent determinant for acquiring *S. aureus* ventilator-associated pneumonia in ICU patients receiving prolonged acute mechanical ventilation [26]. The aim of this study was therefore to investigate the impact of energy deficit on the microbiological results of the blood cultures of prolonged acute mechanically ventilated patients who experienced a first ICU-BSI episode.

Methods

Patients and study design

This prospective, observational, cohort study was conducted from January 2004 to December 2012 in the 18-bed medical ICU of a tertiary teaching hospital. Because of the observational design, no local institutional review board authorization was required according to French bioethics laws. The study was approved by the Commission Nationale de l'Informatique et des Libertés to use the computerized medical data with protection of patient confidentiality. Adult patients intubated at ICU admission and mechanically ventilated for at least 96 h before a first ICU-BSI episode were eligible for analysis. Exclusion criteria included previous episodes of nosocomial bloodstream infection during the current hospital stay, and the rare cases of total parenteral nutrition, thus limiting bias in the analysis of the risk factors for ICU-BSI. All study patients were ventilated with an Evita 4 ventilator (Dräger Medical, Antony, France). Enteral nutrition (EN) (Fresubin Original®, Fresenius-Kabi, France, 0.9 kcal/ml, 55 % carbohydrates, 35 % lipids, and 15 % proteins) was to be started within 24 h of ICU admission, and increased in accordance with the recommendations of the Société de Reanimation de Langue Française as detailed elsewhere [18]. Combining enteral with parenteral nutrition was not used during the study period. When required, glycemia control was achieved by insulin infusion with a glucose cut-off value of 8 mmol/l. Systematic precise nutritional intake (daily estimation of resting energy expenditure (REE), energy-calorie prescribed and delivered) was calculated from ICU admission to day of ICU-BSI to focus our investigations on the early level of energy balance and its impact on the pathogen(s) responsible for ICU-BSI.

ICU-acquired bloodstream infections

ICU-BSI was defined as onset of infection and at least one positive blood culture result unrelated to an infection incubating at ICU admission occurring after 48 h of ICU stay [4]. All blood cultures (BacT ALERT®, Biomérieux Inc, Durham, NC) were obtained from peripheral blood samples by trained nurses. ICU-BSI not related to another site of infection was classified as primary. ICU-BSI related to a causative source of infection (lung, intra-abdominal, urine, soft tissue, and intravascular catheter) was classified as secondary. Catheter-related infections were documented by quantitative tip cultures. Multidrug-resistant microorganisms were defined as methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci, third-generation cephalosporins-resistant *Enterobacteriaceae*, imipinem/ceftazidine- or fluoroquinolones-resistant *Pseudomonas aeruginosa*, and

ticarcillin-resistant *Acinetobacter baumannii* according to national [27] and local Anti-Infectious Comities definitions. Coagulase-negative *Staphylococcus* bacteremia and polymicrobial ICU-BSIs were excluded from analysis, thereby limiting confounding.

Energy balance

Total energy prescribed was calculated from glucose infusions and EN prescriptions. Energy really delivered daily included energy from enteral feeding and glucose infusions. Propofol was not used for continuous sedation. Because indirect calorimetry was not available for every patient, the daily REE was calculated with the following validated equation, incorporating static and dynamic biometric parameters that measure the highly variable and rapidly changing REE (kcal/day) of critically ill patients [18, 26]: $8 \times$ body weight (kg) $+ 14 \times$ height (cm) $+ 32 \times$ minute ventilation (l/min) $+ 94 \times$ body temperature (°C) $- 4{,}834$. Every day from ICU admission to day of ICU-BSI, the following data were collected from charts: weight measured with an electronic scale, temperature (mean of four values measured electronically at 6-h intervals), and minute ventilation (mean of four values determined with the respiratory device at 6-h intervals). Height, assessed with measuring tape and the patient lying in a supine position, was collected at ICU admission. Every day, from ICU admission to day of ICU-BSI, energy balance (energy-calorie really delivered minus REE) was calculated. Since the length of stay from ICU admission to ICU-BSI was not constant, cumulated energy balance was expressed per day of ICU stay before ICU-BSI, thereby limiting temporal relationship. Stored energy (adipose tissue, intramuscular triglycerides, and blood fatty acids or triglycerides) was ignored for the calculation of energy balance [28].

Patient data

Baseline demographic data at the time of ICU admission included age, smoking status, immune deficiencies (corticosteroids, diabetes, cancer treatment, transplants, others), main diagnosis, and simplified acute physiology score (SAPS) II. Protein-calorie malnutrition at ICU admission was assessed by the nutritional risk score (NRS) and actual weight less than 90 % of ideal body weight [16, 29, 30]. Other risk factors for nosocomial infections (prior antibiotics or prior hospitalization within 3 months, previous colonization with multidrug-resistant pathogens or carriage of multidrug-resistant bacteria screened at ICU admission in high-risk patients by using rectal swabs, central venous catheters, transfusions of blood products, days on mechanical ventilation, hemodialysis), days with EN interruptions due to gastrointestinal intolerance or ICU procedures, and days on medications that could diminish nutrient absorption or limit the prescribed feeding-rate volume were assessed from ICU admission to the day of ICU-BSI [18, 26].

Statistical analyses

Results are expressed as numbers (%), means ± SD, or medians (range) for data with non-normal distributions. The sample size was calculated a priori on the basis of the following assumptions: an expected minimal difference in energy deficit of 250–500 kcal/day between groups has clinical relevance. To detect such differences, using a β risk of 0.20, an α error of 0.05, and an energy deficit SD close to 250 kcal/day, at least 34 patients (17/group) for a difference of 250 kcal/day or 12 patients (6/group) for a difference of 500 kcal/day are required. Between groups comparisons used Student's t test for normally distributed variables. Non-normally distributed variables were compared with the Mann–Whitney U test. Fisher's exact test was applied for comparisons of categorical variables. Factors with a significance of $p < 0.20$ in the univariate analysis were considered for multivariate analysis. Logistic regression was used for multivariate analysis. Relationships between pathogen-positive blood cultures and energy-deficit quartiles were assessed using analysis for linear trends in proportion (Mantel–Haenszel test). Statistics were calculated with the StatView 4.5 (Abacus Concept Inc., Berkeley, CA, USA) and EPI INFO 3.4 (Centers for Disease Control and Prevention, Atlanta, GA, USA) software. $p < 0.05$ was considered significant.

Results

Patients and blood cultures

During the study period, 92 patients intubated at ICU admission and on mechanical ventilation for at least 96 h before a first ICU-BSI episode were eligible for analysis. The main characteristics of the studied patients and usual risk factors for nosocomial infections are summarized in Table 1, which also details the nutritional intake results from ICU admission to day of ICU-BSI. Among the 92 episodes of positive blood cultures, 36 were due to *Enterobacteriaceae* (*Escherichia coli*, $n = 18$; *Klebsiella pneumoniae*, $n = 6$; *Proteus mirabilis*, $n = 5$; *Enterobacter cloacae*, $n = 3$; *Citrobacter koseri*, $n = 2$; *Morganella morganii*, $n = 1$; *Serratia marcescens*, $n = 1$), 25 grew *Staphylococcus aureus*, 10 *Pseudomonas aeruginosa*, 10 *Streptococcus* spp. (*Streptococcus pneumoniae*, $n = 3$; *Streptococcus mitis*, $n = 3$; *Streptococcus anginosus*, $n = 2$; *Streptococcus oralis*, $n = 1$; *Streptococcus constellatus*, $n = 1$), six *Enterococcus faecalis*, three *Bacteroides fragilis*, one *Acinetobacter baumannii*,

Table 1 Patients characteristics

Variable	Total population ($n = 92$)	MRSA ICU-BSI ($n = 9$)	ICU-BSI due to other pathogens ($n = 83$)
Characteristics at ICU admission			
Age (years)	69 ± 14	71 ± 15	69 ± 14
Male sex	54 (58.6)	5 (55.5)	49 (59)
Smoking	29 (31.5)	2 (22.2)	27 (32.5)
Immune status			
Systemic corticosteroids ≥4 weeks	25 (27.2)	1 (11.1)	24 (28.9)
Diabetes	21 (22.8)	3 (33.3)	18 (21.7)
Receiving treatment for cancer	16 (17.4)	3 (33.3)	13 (15.66)
Transplant	3 (3.2)	0 (0)	3 (3.6)
Others	7 (7.6)	1 (11.1)	6 (7.2)
Leukocytes, 10^3/ml	15.4 ± 9	15.6 ± 9.2	13.3 ± 9.1
Lymphocytes, 10^3/ml	1.2 ± 1.2	1.1 ± 0.6	1.2 ± 1.2
Weight (kg) mean ± SD	67.7 ± 16.1	63.3 ± 12.1	68.1 ± 16.5
Weight < 90 % of ideal body weight (kg)	18 (19.6)	3 (33.3)	15 (18.1)
BMI (kg/m^2)	23.9 ± 5.1	22.4 ± 3.8	24.1 ± 5.2
NRS	4 (3–7)	6 (3–7)*	4 (3–7)
Reasons for ICU admission			
Acute respiratory failure	46 (50)	6 (66.7)	40 (48.2)
Septic shock	13 (14.2)	1 (11.1)	12 (14.4)
Cardiac arrest	15 (16.3)	0	15 (18.2)
Neurologic failure (nontraumatic)	10 (10.9)	1 (11.1)	9 (10.8)
Cardiogenic shock	4 (4.3)	0	4 (4.8)
Acute renal failure	3 (3.2)	1 (11.1)	2 (2.4)
Postoperative complications	1 (1.1)	0	1 (1.2)
SAPS II at ICU admission	66 ± 20	71 ± 21	66 ± 20
Total length of ICU stay (days)	20 (5–109)	26 (12–40)*	19 (5–109)
Intubation duration before NBI (days)	9 (4–28)	12 (4–18)	9 (4–28)
ICU mortality	75 (81.5)	7 (77.7)	68 (81.9)
Risk factors for nosocomial infections			
Prior hospitalization ≤3 months	52 (56.5)	5 (55.5)	47 (56.6)
Hospital stay before ICU admission (days)	1 (0–56)	7 (0–-41)	1 (0–56)
Prior antibiotics ≤3 months	44 (47.8)	5 (55.5)	39 (46.9)
Colonization with MDR microorganism	8 (8.6)	1 (11.1)	7 (8.4)
Hemodialysis	49 (53.2)	4 (44.4)	45 (54.2)
Transfusions	57 (61.2)	6 (66.6)	51 (61.4)
Transport out of the ICU	63 (68.4)	7 (77.7)	56 (67.4)
Central venous catheter	90 (97.8)	8 (88.8)	82 (98.7)
Positive blood culture	1 (1–7)	2 (1–5)	1 (1–7)
Conditions potentially limiting EN[a] (days)			
Morphine before NBI	5 (0–28)	4 (2–6)*	6 (0–28)
Sedation before NBI	6 (0–28)	4 (2–6)*	6 (0–28)
Myorelaxant before NBI	1 (0–24)	1 (0–2)	1 (0–24)
Vasoconstrictors before NBI	4 (0–24)	4 (1–12)	4 (0–24)
Gastrointestinal intolerance before NBI	1 (0–12)	2 (0–12)*	1 (0–11)
Energy from[b] ICU admission			
Prescribed (kcal/day)	1,054 ± 306	755 ± 282#	1,086 ± 291
Delivered (kcal/day)	877 ± 321	547 ± 232#	912 ± 309
Calculated REE (kcal/day)	1,912 ± 264	1,886 ± 157	1,915 ± 274
Energy balance (kcal/day)	−1,034 ± 402	−1,348 ± 260#	−1,000 ± 401
Energy balance (kcal/kg/day)	−15 ± 5	−21 ± 3†	−14 ± 5

Data are presented as mean ± SD, median (range), or number (%)
BMI body mass index, *EN* enteral nutrition, *ICU* intensive care unit, *MDR* multidrug-resistant, *MRSA* methicillin-resistant *Staphylococcus aureus*, *ICU-BSI* ICU-acquired bloodstream infection, *NRS* nutrition risk score [30], *REE* resting energy expenditure calculated with the Faisy-Fagon 2003 equation [41], *SAPS II* simple acute physiology score
* $0.05 < p < 0.20$, # $p < 0.01$, † $p < 0.001$ MRSA vs other pathogens

[a] Situations that could diminish nutrient absorption or limit the prescribed feeding-rate volume

[b] Energy balance was calculated on the time of ICU-BSI as follows: cumulated energy-calorie really delivered − cumulated REE. Cumulated energy from ICU admission to day of ICU-BSI was normalized by the duration of ICU stay (or intubation duration) before ICU-BSI

Table 2 Relationships between patient energy balance (kcal/day) according to pathogen status in blood cultures

Pathogen responsible for ICU-BSI	Energy balance from ICU admission to day of ICU-BSI	
	Pathogen positive (*n*)	All other pathogens (*n*)
Gram-negative pathogen		
Enterobacteriaceae[a]	−1,027 ± 466 (36)	−1,038 ± 360 (56)
Pseudomonas aeruginosa	−909 ± 280 (10)	−1,049 ± 413 (82)
Bacteroides fragilis	−1,172 ± 347 (3)	−1,029 ± 405 (89)
Acinetobacter baumannii	−1,120 (1)	−1,039 ± 402 (91)
Fusobacterium	−632 (1)	−1,033 ± 404 (91)
Gram-positive pathogen		
Staphylococcus aureus	−1,084 ± 420 (25)	−1,015 ± 397 (67)
MSSA	−936 ± 425 (16)	−1,054 ± 397 (76)
MRSA	−1,348 ± 260 (9)*	−1,000 ± 401 (83)
Streptococcus spp.[b]	−884 ± 249 (10)	−1,052 ± 414 (82)
Enterococcus faecalis	−1,208 ± 234 (6)	−1,015 ± 405 (86)

Data are presented as mean ± SD (number)
ICU intensive care unit, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-sensitive *Staphylococcus aureus*, *ICU-BSI* ICU-acquired bloodstream infection. * $p < 0.01$ compared with other patients
[a] Distribution: *Escherichia coli*, $n = 18$; *Klebsiella pneumoniae*, $n = 6$; *Proteus mirabilis*, $n = 5$; *Enterobacter cloacae*, $n = 3$, *Citrobacter koseri*, $n = 2$; *Morganella morganii*, $n = 1$; *Serratia marcescens*, $n = 1$
[b] Distribution: *Streptococcus pneumoniae*, $n = 3$; *Streptococcus mitis*, $n = 3$; *Streptococcus anginosus*, $n = 2$; *Streptococcus oralis*, $n = 1$; *Streptococcus constellatus*, $n = 1$

and one *Fusobacterium*. Nineteen microorganisms isolated from blood cultures were considered as multidrug-resistant: MRSA, $n = 9$; *Escherichia coli*, $n = 3$; *Klebsiella pneumonia*, $n = 2$; *Pseudomonas aeruginosa*, $n = 1$; *Proteus mirabilis*, $n = 1$; *Enterobacter cloacae*, $n = 1$; *Acinetobacter baumannii*, $n = 1$; *Serratia marcescens*, $n = 1$. Twenty ICU-BSI were classified primary. Among the 72 secondary ICU-BSI, the causative source of infection was ventilator-associated pneumonia in 39 cases, 10 were intra-abdominal, nine were catheter-related infections, nine soft tissues, and five urinary tract.

Energy balance and pathogens responsible for ICU-BSI

Energy balance did not differ significantly between patients infected with Gram-positive ($n = 41$) or Gram-negative ($n = 51$) pathogens (−1,068 ± 379 vs −1,007 ± 421 kcal/day from ICU admission to day of NBI, $p = 0.39$). As shown in Table 2, patients with MRSA ICU-BSI had a significantly higher mean energy deficit than those with positive blood cultures due to other pathogens. Energy balance was not associated with the multidrug resistance of isolated microorganism (−1,131 ± 444 for 19 patients with ICU-BSI caused by multidrug-resistant pathogens vs −1,009 ± 390 kcal/day for 73 patients with ICU-BSI due to non-multidrug-resistant pathogens, $p = 0.24$) or with the causative source of infection (−1,175 ± 392 for 20 patients with primary ICU-BSI vs −995 ± 399 kcal/day for 72 patients with secondary ICU-BSI, $p = 0.07$). Energy balance was comparable for patients with ($n = 51$) or without ($n = 41$) immune deficit (−1,053 ± 366 vs −1,010 ± 447 kcal/day, $p = 0.47$).

Factors associated with MRSA ICU-BSI

Patients with MRSA blood cultures had similar characteristics and risk factors for nosocomial infections to those with ICU-BSI due to other microorganism(s) (Table 1). Primary/secondary ICU-BSI ratio did not differ significantly between patients with MRSA positive blood cultures and those with positive blood cultures due to other microorganism(s) (3/6 and 17/66, respectively, $p = 0.40$). Nutritional status at ICU admission, conditions potentially limiting EN, REE, and intubation duration before ICU-BSI were similar for the two groups. However, patients with MRSA ICU-BSI had lower prescribed or delivered energy, resulting in higher energy deficits (Table 1). Patients with MRSA ICU-BSI had a daily energy deficit higher than those with ICU-BSI due to other microorganism(s) and that difference was statistically significant from day 4 of mechanical ventilation (Fig. 1). Logistic regression analysis identified energy balance as being independently associated with MRSA positive blood cultures (Table 3). The estimated odds ratios for MRSA-positive blood culture associated with an increase in energy deficit of 250 or 500 kcal/day from ICU admission to ICU-BSI were respectively 2.12, 95 % CI [1.28–3.40] and 4.48, 95 % CI [1.65–11.58]. An increasing trend for MRSA-positive blood cultures across the energy-deficit quartiles estimated between ICU admission and day of ICU-BSI was found with the Mantel–Haenszel test (Fig. 2).

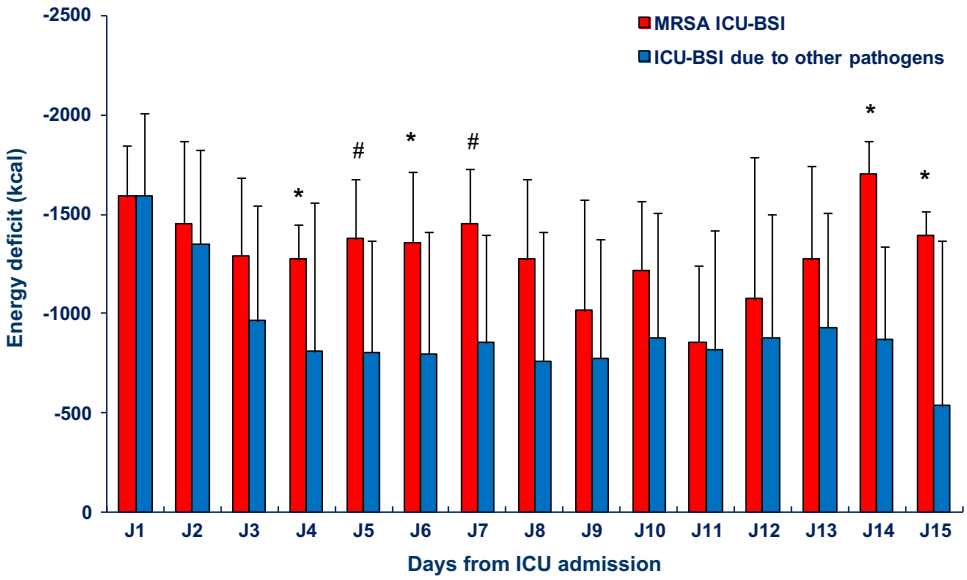

Fig. 1 Evolution of daily energy deficit of patients with MRSA ICU-BSI ($n = 9$) and those with ICU-BSI due to other microorganism(s) ($n = 83$). *ICU* intensive care unit, *MRSA* methicillin-resistant *Staphylococcus aureus*, *ICU-BSI* ICU-acquired bloodstream infection. Values are means with their standard deviations depicted by *vertical bars*. $^{*}p < 0.05$, $^{\#}p < 0.01$ MRSA vs other pathogens

Table 3 Logistic model coefficients table for MRSA-positive blood culture (based on 92 patients) (multivariate analysis)

Variable	Logistic regression coefficient	Standard error	Odds ratio [95 % CI]	*p* value
Constant	−9.09	3.17	0 [0–0.05]	0.004
NRS at ICU admission	0.59	0.32	1.82 [0.96–3.46]	0.07
Total length of ICU stay (days)	0.03	0.02	1.03 [0.98–1.08]	0.15
Morphine before ICU-BSI (days)	0.85	2.9	2.35 [0–700]	0.76
Sedation before ICU-BSI (days)	−1.13	2.9	0.32 [0–95.6]	0.69
Gastrointestinal intolerance before ICU-BSI (days)	0.26	0.14	1.30 [0.98–1.73]	0.07
Cumulated energy balance from ICU admission (kcal/day)	0.003	0.001	1.003[a] [1.001–1.005]	0.01

CI confidence interval, *ICU* intensive care unit, *MRSA* methicillin-resistant *Staphylococcus aureus*, *ICU-BSI* ICU-acquired bloodstream infection, *NRS* nutrition risk score [30]

[a] Indicating the odds ratio for MRSA-positive blood culture of 1.003 is associated with an increase in energy deficit of 1 kcal/day from ICU admission to ICU-BSI. The estimated odds ratios associated with an increase in energy deficit of 250 or 500 kcal/day, i.e., clinically relevant values, are respectively 2.12, 95 % CI [1.28–3.40] and 4.48, 95 % CI [1.65–11.58], yielding an approximate increase in risk to acquire MRSA-positive blood culture

Discussion

The results of this study demonstrated that large negative energy balance was independently associated with MRSA ICU-BSI. This study confirms previous data indicating that early energy deficit is a risk factor for acquiring *Staphylococcus aureus* infectious complications in the ICU [26]. The relationship between chronic PEM and *Staphylococcus aureus* infections was identified a century ago in malnourished children in developing countries. Chronic PEM leads to T lymphocyte deficiency and impaired immune regulation and worsens mucous membrane oxidative stress and barrier defects, causing changes in microbial flora and increasing susceptibility to bacterial and viral infections. The increasing trend for MRSA acquisition across energy-deficit magnitudes herein suggests that acute caloric insufficiency favors MRSA ICU-BSI in critically ill patients through other mechanisms.

The magnitude of the gap between calculated REE and prescribed energy intakes was unexpected considering the procedures used to enable adequate feeding. The present result may be explained, at least in part, by the inclusion of very seriously ill patients with a high incidence of clinical situations predisposing to gastroparesis or interruption of feeding. Another explanation may be the relatively high incidence of renal failure in our patients necessitating limitation of feed volume to limit fluid overload. Additionally, the duration of EN interruptions for procedures or severe gastrointestinal intolerance could explain the differences between delivered and prescribed energy-calories. However, more than 70 % of the energy prescribed was delivered, suggesting that energy deficit was not mostly caused by nursing practices. We conclude that unintentional underestimation of energy-calorie requirements, delay in starting or increasing EN, and overprecautionary interruptions in EN resulted in

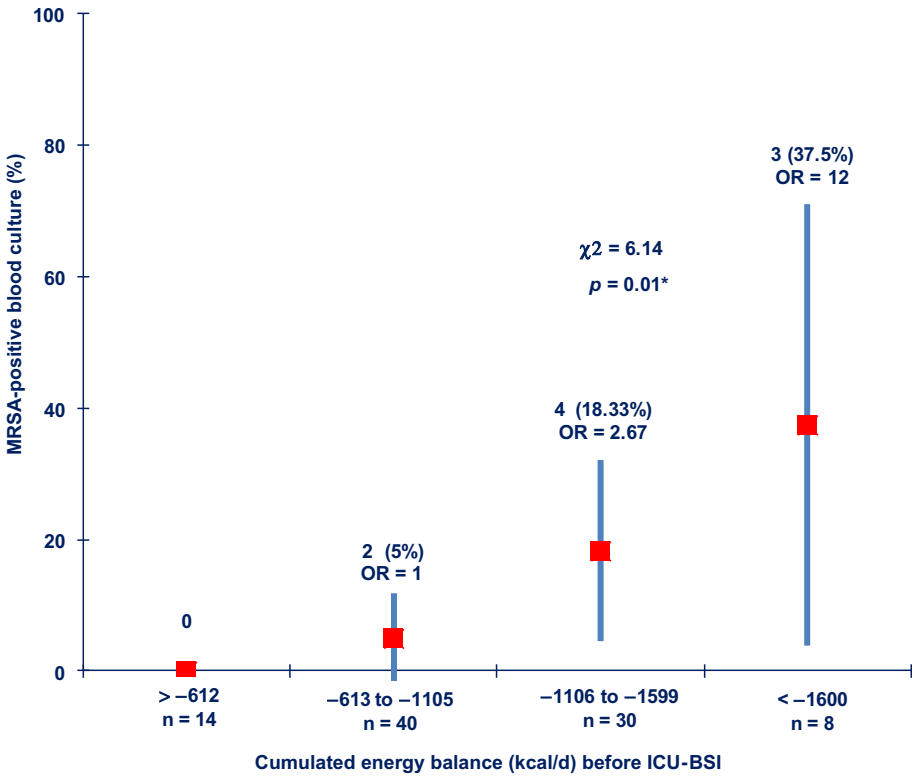

Fig. 2 Relationship between MRSA-positive blood culture and cumulated energy-deficit quartiles estimated between ICU admission and day of positive blood culture for 92 patients with a first episode of ICU-BSI. *ICU* intensive care unit, *MRSA* methicillin-resistant *Staphylococcus aureus*, *ICU-BSI* ICU-acquired bloodstream infection, *OR* odds ratio (comparison vs second quartile). Values are expressed as percentages with 95 % confidence intervals (*blue vertical lines*). Cumulated energy from ICU admission to day of ICU-BSI was normalized by the duration of ICU stay (or intubation duration) before ICU-BSI. *Asterisk* statistics were assessed with the analysis for linear trends in proportion (Mantel–Haenszel test)

underfeeding in our ICU patients. Our findings illustrate the gap between evidence and practice ("the true life") for EN support in the most severely injured patients. Finally, the present observational study indicates that the gap between recommended nutrition care and practice regarding enteral feeding still exists and it results from lack of knowledge and interest of the importance of nutritional assessment by nurses and doctors.

The rate of MRSA ICU-BSI in our patient population and the proportion of primary/secondary ICU-BSI are consistent with the literature data [3–5, 10]. Risk factors for acquisition of *Staphylococcus aureus* bacteremia are prior colonization, severity of underlying disease, previous antibiotics use, length of hospital stay, older age, chronic hemodialysis, and immune deficiency, while the risks for acquiring MRSA infection appear to be dominated by the presence of patients colonized with MRSA in the same ICU, previous antibiotic use, and central venous catheter insertion [11]. MRSA is one of the leading causes of nosocomial infection associated with higher mortality and costs. That is why infection control programs based on identification and isolation of MRSA-colonized or MRSA-infected patients, antibiotic policy, hand hygiene, and care of central venous catheters have been underway for more than a decade with contrasting results depending on the type of patients, geographic area, and local settings [31, 32]. Indeed, traditional MRSA control methods have focused on the prevention of cross-transmission, while the majority of nosocomial infections seem to be of endogenous origin [33]. Host responses to infection are commonly pathogen specific in animals and humans. In this way, the present findings suggest that early in-ICU energy deficit is an MRSA ICU-BSI risk factor readily accessible to preventive measures by limiting large energy deficit the first week of ICU stay in acute chronic critically ill patients.

Clinical and experimental evidence supporting that caloric insufficiency is associated with *Staphylococcus aureus* methicillin resistance remain scarce. In a previous study, we found that the link between early in-ICU energy deficit and *Staphylococcus aureus* ventilator-associated pneumonia was independent of methicillin sensitivity [26]. Differences between ventilator-associated pneumonia and ICU-BSI pathogenesis may explain, at least in part, this apparent discrepancy. Indeed, staphylococcal adhesion on abiotic surfaces, such as central venous catheters, is mediated by the expression of microbial surface component-recognizing adhesive matrix molecules and the production of polysaccharide intercellular adhesins leading to bacterial aggregation and biofilm production [34]. In contrast, damage or destruction of the respiratory epithelium by exotoxins is a necessary condition for fostering the adhesion of *Staphylococcus aureus* on epithelial basal membrane.

The regulation of many *Staphylococcus aureus* virulence determinants by host nutrient availability has been extensively examined [35]. Acute environmental and nutritional stresses, such as pulses of carbon availability,

markedly affect the modulation of staphylococcal virulence determinants via catabolite control protein A (CcpA) repression, a transcriptional regulator, leading to biofilm production and biosynthesis of capsular polysaccharides or toxigenic proteins like α-toxin or toxic shock syndrome toxin-1 [35, 36]. Other regulators, such as *Agr*, *CodY*, or *atl*, are stimulated by changes in nutrient substrates, increasing *Staphylococcus aureus* virulence [35, 36]. However, there is no evidence that MRSA is more virulent than MSSA [37]. To date, no data support that carbohydrate availability may regulate the staphylococcal chromosomal cassette *mec* (SCC*mec*), which encodes *Staphylococcus aureus* resistance to β-lactams and other antibiotics [38]. However, *MgrA*, a multiple gene regulator controlling several efflux systems that confer *Staphylococcus aureus* resistance to antibiotics, is modulated by host nutrient availability [35]. In addition, *Staphylococcus aureus* expresses nitrogen-dependent regulators as *GlnR* that regulates glutamine synthetase, which is important for maintaining methicillin resistance in MRSA [35], suggesting the possibility of pharmaconutrition intervention for optimizing MRSA ICU-BSI prevention in critically ill patients [39]. Further investigations are needed to determine how acute energy deficits and pulses of nutrient availability facilitate *Staphylococcus aureus* resistance to antibiotics and promote virulence characteristics favoring ICU-BSI caused by MRSA in humans.

A limitation of this study is the relatively small sample of MRSA ICU-BSI and caution is needed before extrapolating the present results beyond our patient population and procedures of enteral feeding. The high ICU mortality rate observed herein is similar to a previous cohort of patients in which a large negative energy balance was an independent determinant of ICU outcome [18], suggesting that limiting early energy deficit should be reserved for the sickest patients. The present investigation was undertaken to compare patients with ICU-BSI caused by different microorganisms, but not patients with and without ICU-BSI. Another possible limitation is REE estimation with a predictive method, even though the equation was validated in mechanically ventilated patients [40]. Nevertheless, indirect calorimetry, the gold standard for REE assessment, is not available everywhere and it has been shown that more than 40 % of mechanically ventilated ICU patients had conditions invalidating calorimetric measurements [41]. Consequently, most current studies comparing measured REE and predicted REE are skewed by lack of clear steady state criteria or quality criteria to validate the calorimetric measurements during the metabolic assessments [18, 40, 41]. In the absence of such criteria, many clinical conditions are responsible for erroneous values of O_2 consumption, CO_2 production, and REE [40, 41]. In addition, most of these research studies fail to address the presentation of data that might influence energy expenditure and CO_2 production: catecholamines, opioid agonists, β_2-agonists, neuromuscular blocking agents, body temperature, type of nutrition (formulation) administered, continuation of enteral feeding during calorimetric measurements, and the mode of mechanical ventilation used. These biases largely explain why there are sometimes large discrepancies between modern multiparametric predictive equation estimates and indirect calorimetry measurements in individuals and group.

Conclusion

Our findings demonstrated that early negative energy balance was an independent determinant of MRSA ICU-BSI in prolonged acute mechanically ventilated patients. Feeding prescriptions based on limiting the energy deficit during the first week of ICU stay could be a way to optimize MRSA ICU-BSI prevention.

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