Gram-negative septic thrombosis in critically ill patients: A retrospective case–control study

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A B S T R A C T

Background: Data on septic thrombosis caused by Gram-negative bacilli (GN-ST) in intensive care unit (ICU) patients are currently limited.
Methods: The aim of this retrospective case–control study (matched 1:3) performed over a 15-month period on ICU patients with bacteraemia, associated (cases) or not (controls) with GN-ST, was to assess 30-day mortality and clinical/microbiological features of GN-ST.
Results: During the study period, 16 patients with GN-ST and 48 controls were analyzed. Polytrauma was the cause of ICU admission in 12 (75%) cases and 22 (46%) controls ($p = 0.019$). In no case of septic thrombosis was surgical debridement performed. The site of venous thrombosis was more frequently in the lower limbs, associated with bone fracture in nine out of 12 (75%) cases. The median duration of bacteraemia (22 days vs 1 day; $p < 0.001$) and time to clinical improvement (15 days vs 4 days; $p < 0.001$) were significantly longer in cases than in controls. On analysis of the receiver operating characteristics (ROC) curve, bacteraemia >72 h was significantly associated with GN-ST (area under the curve (AUC) 0.95, sensitivity 0.996 and specificity 0.810; $p < 0.001$). Finally, 30-day mortality was 20% in cases and 67% in controls ($p < 0.001$).
Conclusions: Critically ill patients with GN-ST showed specific clinical features. Despite delayed bacteraemia clearance, targeted antibiotic therapy plus anticoagulation usually provided clinical improvement and a low 30-day mortality rate.

Introduction

Suppurative or septic thrombophlebitis refers to a condition characterized by venous wall inflammation and thrombosis associated with prolonged bacteraemia, and is usually encountered in patients with defined underlying conditions such as the presence of an intravascular device, burns, and malignancy (Fowler et al., 2015; Fry et al., 1994; Gillespie et al., 2000; Hammond et al., 1988; Mermel et al., 2009; Phua et al., 2019; Pruitt et al., 1970). The term 'septic thrombosis' has been adopted recently to describe intravascular device-related *Staphylococcus aureus* bacteraemia, likely sustained by secondary thrombus contamination (Wilson Dib et al., 2018). In older series, bacteraemia associated with thrombus infection has been described as a life-threatening disease, with a reported incidence in critical care settings of 4% and an attributable mortality of approximately 80% (Hammond et al., 1988; Pruitt et al., 1970).

Principles of treatment in septic thrombophlebitis are not well defined and include source control (such as removal of the intravascular device and/or surgical debridement), appropriate antimicrobial chemotherapy, and anticoagulation (Andes et al., 1998; Baker et al., 1979; Fowler et al., 2015; Hammond et al., 1988). Moreover, with the exception of a very old series (Pruitt et al., 1970), no data are presently available in the literature on Gram-negative bacteraemic septic thrombosis (GN-ST).

The aim of this study was to perform an analysis of patients with GN-ST admitted to the intensive care unit (ICU), in order to identify pathogenetic, diagnostic, and therapeutic aspects of the disease in a case–control study.

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Patients and methods

Eligibility criteria and data collection

This was a retrospective, observational, case–control study conducted at the University Hospital Policlinico Umberto I in Rome, Italy. From January 2017 to March 2018, all patients admitted to the ICU were evaluated daily by two dedicated infectious disease consultants (MV and GC) and underwent appropriate microbiology investigations, including follow-up blood cultures (FUBCs) during antibiotic therapy in cases with diagnosed bacteraemia. For patients with a duration of bacteraemia ≥48 h after endovascular indwelling device removal, additional FUBCs were performed every 24 h or 48 h regardless of persistence of fever, until microbiological clearance was achieved in blood cultures.

Patients who fulfilled the following criteria were enrolled as GN-ST cases: (1) laboratory-confirmed persistent Gram-negative bacteraemia; (2) no pulmonary, urinary, intracardiac (negative echocardiography scans), or other recognized sources of infection; (3) venous thrombosis in at least one anatomical site (i.e., supra-aortic trunks, upper or lower limbs, abdomen) assessed by Doppler ultrasound and/or computed tomography angiography (CTA).

All cases were evaluated by a vascular surgeon who ruled out the need for surgical debridement. In addition to antibiotic chemotherapy, all patients with GN-ST received anticoagulation. A regimen of low molecular weight heparin was administered to all patients with a glomerular filtration rate (GFR) >30 ml/min. For patients with severely impaired renal function (GFR ≤ 30 ml/min), unfractionated heparin was administered.

Moreover, thromboprophylaxis was performed routinely in all critically ill patients in consideration of the high risk of them developing a venous thromboembolism or pulmonary embolism; pharmacological interventions, mechanical methods, or both were used. Standard pharmacological prophylaxis with enoxaparin as recommended in the guidelines and mechanical thromboprophylaxis using graduated compression stockings were adopted (Ejaz et al., 2018).

Patients admitted to the ICU during the same period with a documented bloodstream infection (BSI) due to Gram-negative bacilli and no evidence of venous thrombosis, were randomly selected as control patients. We opted for a 1:3 ratio for matching cases to controls. The study protocol was approved by the hospital ethics committee. Considering the retrospective and observational nature of the study, patient informed consent was waived.

The following information was collected: demographic characteristics, comorbidities, Charlson Comorbidity Index, infection-related features (fever, severity of illness, microbiological data, source of infection, source control, procalcitonin (PCT) value at the time of the first positive blood culture and thereafter), the duration and appropriateness of antimicrobial chemotherapy, administration of treatments other than antimicrobials, duration of ICU and hospital stay, and outcome.

Definitions

Fever was defined as a body temperature ≥38 °C in at least two consecutive measurements. Infections were defined according to the standard definitions of the European Centre for Disease Prevention and Control (ECDC)(Annual epidemiological report on vaccine-preventable diseases – invasive bacterial diseases. European Centre for Disease Prevention and Control. 2014. Stockholm, Sweden., 2014). The duration of bacteraemia (days) was calculated by subtracting the date of first positive blood culture from the latest date of positive blood culture growing the same microorganism, according to Canzoneri et al. (2017).

Persistent bacteraemia was defined as repeatedly positive blood cultures after at least 96 h of appropriate antibiotic treatment and at least 48 h since the removal of all potentially infected endovascular devices. Clinical improvement was defined as resolution of fever and no evidence of organ dysfunction attributable to infection, along with weaning from vasopressors and a reduction in serum PCT below the cut-off value of 0.5 ng/ml. Multidrug-resistant (MDR) bacteria were defined according to Magiorakos et al. (2012).

Empirical antibiotic therapy, administered promptly after blood cultures were taken, and definitive antibiotic therapy (drugs in definitive therapy had to have been administered for at least 50% of the total duration of therapy) were defined as appropriate if the isolate turned out to be susceptible to at least one active administered antibiotic or colistin in the case of MDR pathogens. Antibiotic combination therapy was defined as the association of at least two compounds with documented activity against Gram-negative bacteria (Doi, 2019; Rodríguez-Baño et al., 2018).

The severity of illness was measured by Pitt Bacteraemia Score, Sequential Organ Failure Assessment (SOFA) score, and Simplified Acute Physiology Score (SAPS II) calculated at the time of admission and on the day of first positive blood culture. Mortality was assessed at 7, 30, and 60 days.

Statistical analysis

All data were analyzed and all graphs were generated using IBM SPSS Statistics version 20. The demographic characteristics of patients were compared using the Mann–Whitney test. Descriptive statistics were calculated, including simple frequencies, proportions, and rates of the given data on each variable. All measurements were recorded as the median value with inter-quartile range (IQR; 25th percentile–75th percentile). Differences in the data were determined by two-tailed Student t-test after acceptance of a normal distribution, determined by Kolmogorov–Smirnov test. For all tests, the level of statistical significance was 0.05. A multivariate analysis was performed according to a stepwise logistic regression model, to examine the relationship between any predictor and the outcome. Finally, discrimination was evaluated using receiver operating characteristics (ROC) curves. The calibration of the model was evaluated by goodness-of-fit Hosmer–Lemeshow Chi-square statistic. Sensitivity, specificity, negative and positive predictive values (with 95% confidence intervals) were calculated.

Results

A total of 16 cases and 48 controls treated in the ICU during the study period were included in the analysis. All enrolled patients had at least one FUBC. The case patients are described in Table 1. Among the control individuals, 19 (39.6%) with positive FUBCs and/or persistent fever despite appropriate antibiotics and central venous catheter (CVC) removal underwent Doppler ultrasound study and/or CTA: this group included three patients with persisting bacteraemia but negative imaging study results for septic thrombosis. Twenty-nine (60.4%) of the 48 controls did not undergo vascular imaging. An endovascular septic focus was ruled out in 22 of these patients because of the short duration of bacteraemia (less than 48 h). The remaining seven control subjects showed persistent bacteraemia caused either by a well-documented source of infection (four patients: two pneumonia and two complicated urinary tract infection) or by extensively or pan-drug-resistant bacilli (three patients).

Among patients with polytrauma and GN-ST, the site of venous thrombosis was frequently in the lower limbs, associated with bone fracture in nine out of 12 cases (75%) (Table 2).

Table 1
Description of patients with Gram-negative septic thrombophlebitis.

Sex, age (years)	Cause of ICU admission	Pathogen	Site of GN-STP	Duration of bacteraemia (days)	Time to clinical improvement (days)	SAPS II ICU admission	Definite therapy	Outcome
M, 38	Polytrauma	CR-*Klebsiella pneumoniae*	Lower limbs	18	16	26	Combination antibiotic therapy	Transfer to surgical ward
F, 62	Head trauma with intracerebral hemorrhage	*Enterobacter aerogenes*	Jugular vein	22	8	44	Combination antibiotic therapy	Death on day 22 due to progression of underlying disease
F, 46	Polytrauma	CR-*Klebsiella pneumoniae*	Lower limbs	48	22	48	Combination antibiotic therapy	Transfer to surgical ward
M, 54	Polytrauma	CR-*Acinetobacter baumannii*	Lower limbs	11	14	38	Combination antibiotic therapy	Transfer to surgical ward
F, 40	Heart failure	CR-*Klebsiella pneumoniae*	Abdominal vessels	13	–	36	Combination antibiotic therapy	Death on day 19 due to progression of underlying disease
M, 32	Polytrauma	CR-*Klebsiella pneumoniae*	Lower limbs	36	20	31	Monotherapy	Transfer to surgical ward
F, 55	Polytrauma	*Providencia* spp	Lower limbs	51	13	36	Combination antibiotic therapy	Transfer to surgical ward
F, 40	Polytrauma	*Enterobacter* spp.	Lower limbs	18	18	20	Monotherapy	Transfer to surgical ward
M, 83	Polytrauma	*Enterobacter* spp.	Lower limbs	22	6	44	Combination antibiotic therapy	Transfer to surgical ward
F, 51	Intracerebral hemorrhage	*Morganella morganii*	Over-aortic trunks	31	25	39	Combination antibiotic therapy	Death on day 80, not due to infection-related causes
M, 57	Polytrauma with intracerebral hemorrhage	*Pseudomonas aeruginosa*	Popliteal vein	6	15	40	Combination antibiotic therapy	Death on day 15 due to septic shock by CR-*Klebsiella pneumoniae*
M, 66	Intracerebral hemorrhage	CR-*Acinetobacter baumannii*	Lower limbs	54	28	41	Combination antibiotic therapy	Death on day 105, not due to infection-related causes
M, 49	Polytrauma	CR-*Klebsiella pneumoniae*	Over-aortic trunks	78	20	31	Combination antibiotic therapy	Transfer to surgical ward
M, 40	Polytrauma	CR-*Acinetobacter baumannii*	Lower limbs	4	11	54	Combination antibiotic therapy	Death on day 83, not due to infection-related causes
F, 59	Polytrauma	*Klebsiella pneumoniae*	Over-aortic trunks	19	6	40	Combination antibiotic therapy	Transfer to surgical ward
F, 65	Polytrauma	CR-*Klebsiella pneumoniae*	Lower limbs	44	12	38	Combination antibiotic therapy	Transfer to surgical ward

BSI, bloodstream infection; CR, carbapenem-resistant; F, female; GN-STP, Gram-negative septic thrombophlebitis; ICU, intensive care unit; M, male; SAPS II, Simplified Acute Physiology Score.

Table 2
Site of thrombosis in patients with and without polytrauma.

Site of thrombosis	Polytrauma	
	Yes (*n* = 12)	No (*n* = 4)
Lower limbs	9 (75%)	2 (50%)
Supra-aortic trunks	3 (25%)	1 (25%)
Abdominal vessels	0 (0%)	1 (25%)

As shown in Table 3, there was no significant difference in age, sex, SOFA score at ICU admission, Pitt Bacteraemia Score, appropriate empirical therapy, or rate of MDR isolates between the cases and controls. Controls were more likely to show a higher Charlson Comorbidity Index and SAPS II score. Polytrauma was the cause of ICU admission in 12 cases (75%) and 22 controls (46%) ($p = 0.019$). *Klebsiella pneumoniae* was the most common etiology in cases (seven patients, 44%) and was less frequent in controls (13 patients, 27%), whereas *Acinetobacter baumannii* was more frequently isolated in controls (16 patients, 33%) than in cases (three patients, 19%). The median length of appropriate antibiotic therapy was 22 days (IQR 14–54 days) for cases and 14 days (IQR 8–16) for controls ($p = 0.023$). The duration of bacteraemia was significantly longer in cases than in controls (22 days, IQR 1–45 days vs 1 day, IQR 1–6 days, respectively; $p < 0.001$). The time to clinical improvement was 15 days (IQR 12–20 days) for cases and 4 days (IQR 1–11 days) for controls ($p < 0.001$). The median duration of fever was 12 days (IQR 7–15 days) for cases and 1 day (IQR 0–7 days) for controls ($p < 0.001$), and patients with GN-ST needed a somewhat longer course of vasopressor support compared to controls ($p = 0.041$).

The ROC curve regarding the duration of bacteraemia as a diagnostic criterion for the development of septic thrombophlebitis is shown in Figure 1. Bacteraemia lasting longer than 72 h was associated with septic thrombophlebitis, with an area under the ROC curve (AUC) of 0.95, a sensitivity of 0.996, and a specificity of 0.810 ($p < 0.001$).

Among GN-ST patients, a median duration of bacteraemia of 14 days (IQR 0–26 days) was observed after clinical improvement; in

Table 3
Comparison of microbiological and clinical features between the study groups—univariate analysis; data are presented as the median (IQR), or n (%).

	Controls (n = 48)	Cases (n = 16)	p-value
Age (years)	59 (45–74)	53 (40–60)	0.094
Female sex	19/48 (40%)	8/16 (50%)	0.243
ICU admission for polytrauma	22/48 (46%)	12/16 (75%)	0.019
Charlson Comorbidity Index ≥5	10/44 (23%)	1/16 (6%)	0.036
SAPS II > 40 at ICU admission	28/46 (61%)	5/16 (31%)	0.018
SOFA at ICU admission	7 (6–10)	9 (7–10)	0.307
Hospitalization within the last 90 days	11/44 (25%)	2/16 (13%)	0.050
Antibiotics within the last 30 days	36/42 (86%)	14/15 (93%)	0.189
GN infection within the last 30 days	18/42 (43%)	1/16 (6%)	<0.001
Pitt Bacteraemia Score	8 (4–8)	7 (6–9)	0.09
Mechanical ventilation	35/44 (80%)	14/16 (88%)	0.178
CRRT	9/44 (20%)	2/16 (13%)	0.228
Acinetobacter baumannii	16/48 (33%)	3/16 (19%)	0.111
Klebsiella pneumoniae	13/48 (27%)	7/16 (44%)	0.128
Enterobacter spp.	6/48 (13%)	3/16 (19%)	0.290
Pseudomonas aeruginosa	5/48 (10%)	1/16 (6%)	0.296
Escherichia coli	3/48 (6%)	0/16 (0%)	0.042
Serratia spp.	2/48 (4%)	0/16 (0%)	0.080
Morganella morganii	1/48 (2%)	1/16 (6%)	0.267
Proteus spp.	1/48 (2%)	0/16 (0%)	0.161
Providencia spp.	1/48 (2%)	1/16 (6%)	0.267
MDR isolate	29/48 (60%)	9/16 (56%)	0.389
Appropriate empirical therapy	24/40 (60%)	7/12 (58%)	0.425
Appropriate definite therapy	34/42 (81%)	4/11 (36%)	0.269
Combination antibiotic therapy	12/49 (29%)	15/16 (94%)	0.054
Duration of appropriate therapy (days)	14 (8–16)	22 (14–54)	0.023
Time to PCT normalization (days)	9 (1–11)	12 (7–15)	0.184
Vasopressor support from FBCs (days)	0 (0–5)	4 (0–11)	0.041
Duration of fever (days)	1 (0–7)	12 (7–15)	<0.001
Days to clinical improvement	4 (1–11)	15 (12–20)	<0.001
Duration of bacteraemia (days)	1 (1–3)	22 (17–45)	<0.001
Persistence of bacteraemia after clinical improvement (days)	N/A	14 (0–26)	N/A
7-day mortality	10/48 (21%)	0/16 (0%)	<0.001
30-day mortality	26/39[a] (67%)	3/15[b] (20%)	<0.001
60-day mortality	28/35[c] (80%)	5/15[b] (33%)	0.002
ICU mortality	27/48 (56%)	6/16 (38%)	0.102

CI, confidence interval; CRRT, continuous renal replacement therapy; FBCs, first blood cultures; GN, Gram-negative; ICU, intensive care unit; IQR, interquartile range; MDR, multidrug-resistant; N/A, not applicable (clinical improvement occurred before bacteraemia clearance); OR, odds ratio; PCT, procalcitonin; SAPS II, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.
[a] Nine patients lost at follow-up.
[b] One patient lost at follow-up.
[c] Thirteen patients lost at follow-up.

contrast, controls showed microbiological clearance of the bacteraemia before clinical improvement (see Figure 2).

Finally, follow-up data were available for 15 (93.7%) of the 16 GN-ST patients and 39 (81.2%) of the 48 controls: the 7-, 30-, and 60-day mortality rates were significantly lower in cases than in controls (p < 0.001, p = 0.002, and p = 0.004, respectively), as reported in Table 3.

Discussion

This appears to be the first description of a case-series of ICU patients with GN-ST. Of importance, the data provide an original perspective about GN-ST. Interestingly, on ROC curve analysis, a duration of bacteraemia >72 h was an important diagnostic criterion for ST. Among GN-ST patients, a median duration of bacteraemia of 14 days was observed after clinical improvement, whereas controls showed microbiological clearance of bacteraemia before clinical improvement. Finally, a standardized approach to GN-ST with anticoagulants and targeted antibiotic therapy was associated with lower mortality when compared to controls.

Generally, so-called septic thrombophlebitis has been classified into four forms: central, cavernous sinus, portal vein, and superficial thrombophlebitis (Fowler et al., 2015). The disease has been classified as a vasculitis with direct invasion of the vascular wall by pathogens, resulting in vein inflammation and thrombosis, and potentially in secondary bacteraemia Fowler et al.,

2015. Microorganisms may gain access to veins via the bloodstream, regional lymphatics, or from a contiguous infective focus. For example, pylephlebitis begins with thrombophlebitis of small vessels draining an intra-abdominal infected site that may extend to larger veins, eventually leading to portal vein involvement (Kumar et al., 2015). Macroscopically, the vein is enlarged, tortuous, and thickened, perivascular suppuration may be associated, and an abscess may develop in the vein wall and lumen (Fowler et al., 2015; Kasper et al., 2005). Microscopically, fibrinoid necrosis of the vessel wall, a leukocyte infiltrate, damage to the endothelium, and occlusion are evident (Strinden et al., 1985), and intramural microabscesses may be present (Witort-Serraglini et al., 1999). Considering pathogenetic mechanisms of the disease, conservative management with antibiotics alone usually fails to eradicate this disease. Curative treatment requires a combination of antimicrobial therapy and surgical control of the primary focus of infection, drainage of abscesses, and in the case of superficial suppurative thrombophlebitis, excision of the involved vein (Barenholtz et al., 1973; Fowler et al., 2015; Laupland, 2007; Pruitt et al., 1970).

In contrast to the classical disease therapy approach, none of our patients with GN-ST underwent surgery. Clinical improvement was achieved after antimicrobial and anticoagulation therapy were established. The study data are in line with the observations of Strinden and co-workers in a small series of eight patients with *Candida* septic thrombosis of the great central veins (Strinden et al., 1985). In

Parameters	Value	Lower Limit	Upper limit	p-value
AUC	0.953	0.900	0.980	<0.001
Sensitivity	0.996	0.870	0.938	-
Specificity	0.810	0.730	0.890	-
Positive Predictive Value	0.593	0.650	0.730	-
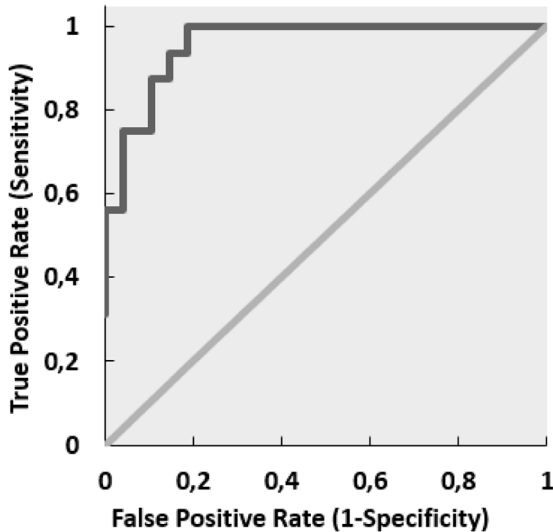
**Figure 1.** ROC curve for duration of bacteraemia >72 h in the development of septic thrombophlebitis.

a recent report of 128 *S. aureus* catheter-related septic thrombosis cases, no mention of surgical debridement was made, while adjunctive anticoagulation therapy was significantly associated with clinical success (Wilson Dib et al., 2018).

The present study data focused on two main aspects: (1) prolonged bacteraemia (>72 h) was found to be the main factor associated to septic thrombosis; the duration of bacteraemia was significantly longer in cases compared to controls (22 days vs 1 day); and (2) the time to clinical improvement was 15 days for cases and 4 days for controls. Several distinct events might have been involved in the pathogenesis of septic thrombosis in our cases. The vein wall might have first been damaged by systemic or regional stresses such as sepsis, endovascular catheter implantation, or local trauma (Stein and Pruitt, 1970). Notably, in the present study, population polytrauma was found to be a major risk factor for GN-ST. No less important, the majority of patients with polytrauma developed lower extremity venous thrombosis, in close proximity to a bone fractured site. Thus, we hypothesize that a venous thrombus might have provided a suitable medium for bacterial entrapment and colonization throughout bacteraemia. This could be similar to the role played by non-bacterial thrombotic endocarditis in the pathogenesis of infective endocarditis (Fowler et al., 2015; Freedman, 1987; Kaplan et al., 2015): during a transient or even subclinical bacteraemia, the venous thrombus might have acted as a nidus, and secondary endovascular infection might have ensued with persistent bacterial seeding in the blood. Considering all of the above, from a pathogenetic perspective, the terms 'septic thrombosis' and even 'phlebothrombitis' might be more appropriate than thrombophlebitis to describe this syndrome featuring an intravascular infection with secondary persistent bacteraemia. Further studies are necessary to confirm these observations.

Critically ill patients, and in particular subjects who have recently experienced a severe accident trauma, are considered at high risk for developing a venous thromboembolism or a pulmonary embolism (Ejaz et al., 2018). In our center, standard prophylaxis strategies were routinely adopted for all patients, comprising a pharmacological intervention, mechanical methods, or both. Nevertheless, the study data seem to suggest that in the polytrauma setting, thromboembolic prophylaxis might more frequently fail, leaving a thrombus as a suitable final destination and nidus of infection with Gram-negative bacilli bacteraemia. Thus, we believe that under these circumstances, an aggressive diagnostic approach should be considered, with active clinical monitoring and radiographic surveillance for the early detection of thrombus lesions that require a prompt switch from prophylaxis to anticoagulant therapy.

As is generally known, early source control has a favorable impact in the management of patients with severe sepsis and septic shock (Martínez et al., 2017). It was found in the present study that among critically ill patients, GN-ST often presented as an endovascular infective syndrome with persistently positive blood cultures and an indolent clinical behavior once appropriate antibiotic treatment and anticoagulation were started. Remarkably, despite the persistence of bacteraemia, both defervescence and a rapid decrease in serum PCT concentration under the cut-off
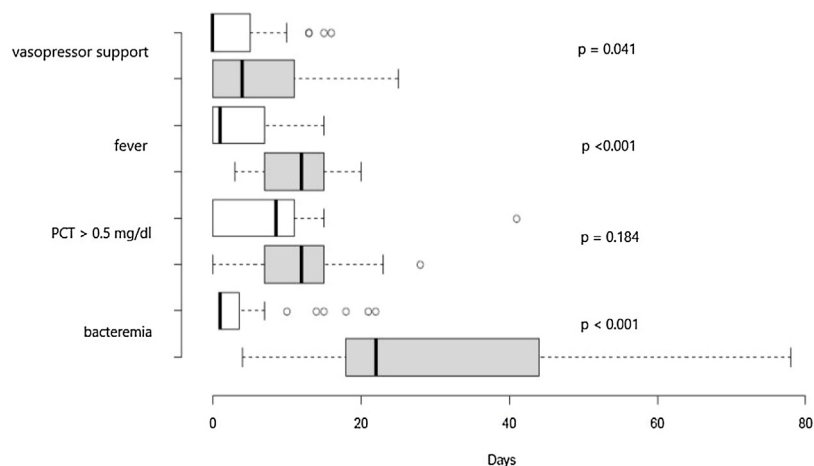
Figure 2. Clinical course of cases (in grey) and controls (in white). PCT: procalcitonin.

value of 0.5 ng/ml were observed, thus confirming our preliminary reports (Ceccarelli et al., 2018; Spaziante et al., 2019, 2018). A possible explanation could be the phenomenon of immune tolerance: this mechanism may induce the selective block of some proinflammatory pathways activated by bacterial endotoxins or cytokines and reduce the production of PCT, which is usually produced in response to inflammatory triggers, favoring a long indolent clinical course even in the presence of microbial eradication failure (Ayres and Schneider, 2008; Yan et al., 2017). In this context, FUBCs should be considered of great importance for the diagnosis of GN-ST. This is a somewhat different perspective from that reported in a non-ICU setting by Canzoneri and co-workers, who stated that FUBCs add little value in the management of patients with bacteraemia caused by Gram-negative bacilli (Canzoneri et al., 2017). As a matter of fact, in our GN-ST series, FUBCs represented the single most important driver for antimicrobial therapy management, especially when defervescence, hemodynamic stability, and PCT normalization had been achieved, in accordance with our previous observations (Spaziante et al., 2019). Finally, a significantly lower mortality was demonstrated in patients with GN-ST compared to patients with Gram-negative bacteraemia only.

In conclusion, this study presents important limitations, considering the retrospective design and the small number of patients included, thus definitive conclusions cannot be drawn. Moreover, the selection of controls could be considered a bias. However, this small series provides some evidence that critically ill patients, particularly those admitted for polytrauma, with a diagnosis of Gram-negative bacteraemia that persists after apparently adequate source control and targeted antibiotic administration, should receive an appropriate diagnostic work-up to exclude a GN-ST. FUBCs until bacteraemia clearance would appear to be mandatory to guide the duration of antimicrobial therapy, and adjunctive anticoagulation seems an essential therapeutic provision in the setting of a septic Gram-negative 'phlebothrombosis'. Finally, strict clinical monitoring of patients at increased risk, such as those with polytrauma, might allow the early detection and therapy of underlying thrombus lesions, thus preventing their possible superinfection during Gram-negative bacteraemia.

Declarations

Ethical approval: This study was approved by the Ethics Committee of the Policlinico Umberto I University Hospital and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent: Each patient was anonymous in the study and the need for consent was waived due to the anonymized data and the retrospective study design.

Conflict of interest: None.

Martina Spaziante and Simone Giuliano contributed equally to the paper.

Author contributions: G.C., S.G., F.A., and M.V. participated in the clinical management of the patients. M.S., G.C., and F.A. collected the clinical data. M.S., S.G., A.R., and M.V. wrote the draft of the manuscript. C.B. performed the statistical analysis. All authors have seen and approved the final version of the manuscript.

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