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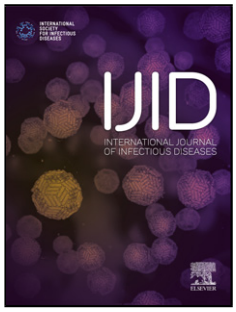

Gram-negative septic thrombosis in critically ill patients: A retrospective case-control study

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PII: S1201-9712(20)30113-2

DOI: https://doi.org/10.1016/j.ijid.2020.02.054

Reference: IJID 4000

To appear in: *International Journal of Infectious Diseases*

Received Date: 13 January 2020

Revised Date: 21 February 2020

Accepted Date: 26 February 2020

Please cite this article as: Spaziante M, Giuliano S, Ceccarelli G, Alessandri F, Borrazzo C, Russo A, Venditti M, Gram-negative septic thrombosis in critically ill patients: A retrospective case-control study, *International Journal of Infectious Diseases* (2020), doi: https://doi.org/10.1016/j.ijid.2020.02.054

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

Running title: Gram-negative bacilli septic thrombophlebitis.

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Word count: 2257

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Highlights

- Few data are available about Gram-negative bacilli septic thrombosis
- In Intensive Care Unit, polytrauma patients are at highest risk for this condition
- Optimal therapeutic approach requires targeted antibiotics plus anticoagulation
- Follow up blood cultures are essential to establish diagnosis and therapy duration

Abstract

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Background: Few data are presently available on Gram-negative bacilli septic thrombosis (GN-ST) in intensive care unit (ICU) patients.

Methods: Retrospective case-control study (matched 1:3) performed on ICU patients with bacteremia associated (cases) or not (controls) to GN-ST over a 15-month period aimed to assess 30-day mortality and clinical/microbiological features of GN-ST.

Results: during 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 ST was performed a surgical debridement; the site of venous thrombosis was more frequently in lower limbs associated with bone fracture in 9 out of 12 (75%) cases. Median duration of bacteremia (22 vs 1 days, p <0.001) and time to clinical improvement (15 vs 4 days, p <0.001) were significantly longer in cases. At ROC curve, a bacteremia >72 hours was significantly associated with GN-ST (AUC 0.95, sensitivity 0.996 and specificity 0.810, p<0.001). Finally, 30-day mortality was 20% in cases and 67% among controls (p< 0.001).

Conclusion: critically ill patients with GN-ST showed specific clinical features. Despite delayed bacteremia clearance, targeted antibiotic therapy plus anticoagulation usually provide clinical improvement and a low 30-day mortality rate.

Keywords. Gram-negative bacteremia; follow-up blood cultures; ICU; septic thrombophlebitis; septic thrombosis; surgical debridement

Introduction

Suppurative or septic thrombophlebitis refers to a condition characterized by venous wall inflammation and thrombosis associated with a prolonged bacteremia, usually encountered in patients with defined underlying conditions such as the presence of an intravascular device, burns, and malignancy (1-7). The term “septic thrombosis” has been recently adopted to describe intravascular-devices related *Staphylococcus aureus* bacteremia, likely sustained by secondary thrombus contamination (8). In old series bacteremias associated to thrombus infection have been described as life-threatening diseases with a reported incidence in critical care settings of 4% and an attributable mortality of approximately 80% (2,4).

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However, principles of treatment are not well defined and include source control (such as removal of the intravascular device and/or surgical debridement), appropriate antimicrobial chemotherapy and anticoagulation (2, 6, 9, 10). Moreover, except a very old series (4) no data are presently available in literature on Gram-negative bacteremic ST (GN-ST).

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

Patients and Methods

Eligibility criteria and data collection

This is a retrospective, observational, case-control study conducted at the University-hospital Policlinico Umberto I of 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 bacteremia. In patients with duration of bacteremia ≥ 48 hours after endovascular indwelling device removal, additional FUBCs were performed every 24 or 48 hours regardless of persistence of fever until microbiological clearance was achieved in BCs.

Patients who fulfilled the following criteria were enrolled as GN-ST cases: 1) laboratory confirmed persistent Gram-negative bacteremia; 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 CT angiography.

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 administrated to all patients with glomerular filtration rate (GFR) > 30 ml/min. In patients with severely impaired renal function (GFR ≤ 30 ml/min) was administered unfractioned heparin.

Moreover, thromboprophylaxis was routinely performed in all critically ill patients in consideration of the high-risk for developing a venous thromboembolism and a pulmonary embolism, using pharmacologic intervention, mechanical methods, or both. Standard pharmacological prophylaxis with enoxaparin as

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recommended by guidelines, and mechanical thromboprophylaxis using graduated compression stockings were adopted (11).

Patients admitted to the ICU during the same period and with 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 and, considering its retrospective and observational nature, patients informed consent was waived.

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

Definitions

Fever was defined as body temperature ≥ 38°C in at least two consecutive measurements.

Infections were defined according to the standard definitions of the European Centers for Disease Control and Prevention (eCDC) (12).

Duration of bacteremia (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 (13).

Persistent bacteremia was defined as repeatedly positive BCs after at least 96 hours of appropriate antibiotic treatment and at least 48 hours since the removal of all potentially infected endovascular devices.

Clinical improvement was defined as fever resolution and no evidence of organ dysfunction attributable to infection, along with weaning from vasopressors and reduction of serum PCT below the cut-off value of 0.5 ng/ml.

Multidrug resistant (MDR) bacteria were defined according to Magiorakos et al. (14).

Empiric antibiotic therapy, early administered after BCs were taken, and definite antibiotic therapy (drugs in definitive therapy must have been administered for at least 50% of the total duration of therapy)

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were defined as appropriate if the isolate turned out to be susceptible to at least one active administered antibiotic or colistin in case of MDR pathogens.

Antibiotic combination therapy was defined as the association of at least two compounds with documented activity against Gram negative bacteria (15-16).

The severity of illness was measured by Pitt bacteremia, SOFA and SAPS II scores 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 analysed and all graphs were generated using Statistical Package for Social Science (SPSS) version 20. The demographic characteristics of patients were compared using Mann–Whitney test. Description of simple frequencies, proportions, and rates of the given data on each variable was calculated. All measurements were taken median and interquartile range (IQR: 75th percentile, 25th percentile). Differences in the data were determined by two-tailed student t-test after acceptance of normal distribution with the Kolmogorov-Smirnov test. In all tests, the level of statistical significance was 0.05. We performed a multivariate analysis according to a stepwise logistic regression, to examine the relationship between the any predictor and outcome. Finally, we evaluated discrimination using receiver operating characteristic curves (ROC). The calibration of the model was evaluated by the goodness-of-fit Hosmer-Lemeshow $\chi 2$ statistic. We calculated sensitivity, specificity, negative and positive predictive values (with 95% confidence intervals).

Results

Overall, during study period 16 cases and 48 controls were included in the analysis. All enrolled patients underwent to at least one FUBC. Cases are described in **Table 1.** Among controls, 19 (39.6%) with positive FUBCs and/or persistent fever despite appropriate antibiotics and CVC removal underwent doppler ultrasound study and/or CT angiography: this group included 3 patients with persisting bacteremia but negative imaging study results for ST. Twenty-nine (60.4%) out of 48 controls did not undergo vascular imaging. In 22 out of these, an endovascular septic focus was ruled out because of the short duration of bacteremia (less than 48 hours). The remaining 7 controls showed persistent bacteremia caused by a well-

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documented source of infection in 4 patients (2 pneumonia and 2 complicated urinary tract infection) and by extensively or pan-drug resistant bacilli in 3 patients.

Among patients with polytrauma and GN-ST, the site of venous thrombosis was frequently in the lower limbs, associated with bone fracture in 9 out of 12 (75%) cases (**Table 2**).

As shown in **Table 3,** no differences about age, sex, SOFA score at ICU admission, Pitt Bacteremia Score, appropriate empirical therapy and rate of MDR isolates between cases and controls were registered. Controls were more likely to show higher Charlson Comorbidity Index and SAPS II score. Polytrauma was the cause of ICU admission in 12 (75%) cases and 22 (46%) controls (p=0.019). *Klebsiella pneumoniae* was the most common etiology in cases (7 patients, 44%) compared to control (13 patients, 27%), whereas *Acinetobacter baumannii* was more frequently isolated in controls (16 patients, 33%) than in cases (3 patients, 19%). Median length of appropriate antibiotic therapy was 22 days (IQR 14-54) for cases and 14 days (IQR 8-16) for controls (p = 0.023). The duration of bacteremia was significantly longer in cases compared to controls (22 days IQR 1-45 vs 1 days IQR 1-6, respectively, p <0.001). Time to clinical improvement was 15 days (IQR 12-20) for cases and 4 days (IQR 1-11) for controls (p <0.001). 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), whereas patients with GN-STP needed somewhat longer (p = 0.041) course of vasopressor support compared to controls.

In **Figure 1** is reported ROC curve about duration of bacteremia as diagnostic criterion for development of STP. A bacteremia longer than 72 hours was associated with STP with an AUC of 0.95, a sensitivity of 0.996 and a specificity of 0.810 (p<0.001).

Among GN-ST patients, a median 14-day bacteremia duration (IQR 0-26 days) was observed after clinical improvement, compared to controls where was reported a microbiological clearance of bacteremia before clinical improvement (see **Figure 2**).

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

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Discussion

To our knowledge this is the first description of a cases series of ICU patients with GN-ST. Of importance, these data provide an original perspective about GN-ST. Interestingly, at ROC curve duration of bacteremia >72 hours was an important diagnostic criterion for ST; among GN-ST patients, a median 14-day bacteremia duration was observed after clinical improvement, compared to controls where was reported a microbiological clearance of bacteremia before clinical improvement. Finally, a standardized approach of GN-ST with anticoagulants and targeted antibiotic therapy was associated with lower mortality, compared to controls.

Classically, so called septic thrombophlebitis has been classified into 4 forms: central, cavernous sinus, portal vein and superficial thrombophlebitis (6). The disease has been classified as a vasculitis with a direct invasion of vascular wall by pathogens, resulting in vein inflammation, thrombosis and, potentially, a secondary bacteremia (6, 14). 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 intraabdominal infected site that may extend to larger veins, eventually leading to portal vein involvement (17). Macroscopically, the vein is enlarged, tortuous and thickened, perivascular suppuration may be associated, and an abscess may develop in vein wall and lumen (6, 18). Microscopically, fibrinoid necrosis of the vessel wall, leukocyte infiltrate, damage of endothelium and occlusion are evident (19) and intramural microabscesses may be present (20). 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 primary focus of infection, drainage of abscesses and, in case of superficial suppurative thrombophlebitis, excision of the involved vein (4, 6, 21-22).

In contrast to classical disease therapy approach, none of our patients with GN-ST underwent surgery: clinical improvement was achieved after antimicrobial and anticoagulation therapy were established. Our data are in line with observations of Strinden and coworkers in a small series of 8 patients with C*andida* septic thrombosis of great central veins (19). In a recent report of 128 *Staphylococcus aureus* catheter related ST, no mention of surgical debridement was made while adjunctive anticoagulation therapy resulted significantly associated to clinical success (2).

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Our data focused on 2 main aspects: a prolonged bacteremia (>72 hours) resulted as the main predisposing factor for development of ST; compared to controls, duration of bacteremia was significantly longer in cases compared to controls (22 days vs 1 day), while 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 ST in our cases. The vein wall might have first been damaged by systemic or regional stresses such as a sepsis, endovascular catheter implantation or local trauma (23). Notably, in our study population polytrauma resulted to be a major risk factor for GN-ST. Not less important, majority of patients with polytrauma developed lower extremities' venous thrombosis, in close proximity to a bone fractured site. Thus, we here hypothesize that venous thrombus might have worked as a suitable medium for bacterial entrapment and colonization throughout bacteremia. This could be similar to the role played by nonbacterial thrombotic endocarditis in the pathogenesis of infective endocarditis (6, 24, 25): during a transient or even subclinical bacteremia, the venous thrombus might have played as a nidus and secondary endovascular infection might have ensued with persistent bacterial seeding in blood. Considering all the above, from a pathogenetic perspective, the terms "septic thrombosis" or even "phlebothrombitis" might be more appropriate than thrombophlebitis to describe this syndrome featuring an intravascular infection with secondary persistent bacteremia. Further studies are necessary to confirm these observations.

The critically ill patients, and in particular subjects who had recently experienced a severe accident trauma, are considered high-risk for developing a venous thromboembolism and a pulmonary embolism (11). Standard prophylaxis strategies were routinely adopted for all patients in our center using pharmacologic intervention, mechanical methods, or both. Nevertheless, our data seem to suggest that in polytrauma setting thromboembolic prophylaxis might more frequently fail leaving a thrombus as suitable final destination and nidus of infection of Gram negative bacilli bacteremia. Thus, we believe that under these circumstances an aggressive diagnostic approach should be considered with active clinical monitoring and radiographic surveillance for early detection of thrombus lesions that require 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 (26). We found that, among critically ill patients, GN-ST often presents as an endovascular infective syndrome with persistently positive BCs and an indolent clinical behavior once

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appropriate antibiotic treatment and anticoagulation were started. Remarkably, despite persistence of bacteremia, not only defervescence but also a rapid decrease of serum PCT concentrations under cut-off value of 0.5 ng/ml have been observed, thus confirming our preliminary reports (27-29). One possible explanation could be offered by phenomenon of immune tolerance: this mechanism may induce the selective blocks of some pro-inflammatory pathways activated by bacterial endotoxins or cytokines and reduce the production of PCT, usually produced in response to inflammatory triggers (30), favouring a long indolent clinical course even in the presence of microbial eradication failure (31-32). In this context, FUBCs should be considered of great importance for the diagnosis of GN-ST. This is a somewhat different perspective from what reported in a non-ICU setting by Canzoneri and coworkers who stated that FUBCs add a little value in the management of patients with Gram-negative bacilli bacteremia (13). 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 have been achieved, accordingly with our previous observations (29). Finally, a significantly lower mortality was demonstrated in patients with GN-ST compared to patients with Gram-negative bacteremia only.

Conclusion

Our study presents an important limitation, considering the retrospective design and the small number of patients that did not consent to reach definite conclusions; moreover, controls selection could be considered a bias. However, our small series provides some evidence that in critically ill patients, particularly if admitted for polytrauma, diagnosis of Gram-negative bacteremia, persisting after an apparently adequate source control and a targeted antibiotic administration, should receive an appropriate diagnostic work-up to exclude a GN-ST. FUBCs until bacteremia clearance seem mandatory to guide antimicrobial therapy duration, and adjunctive anticoagulation seems an essential therapeutic provision in the setting of a septic Gram-negative "phlebothrombitis". Finally, strict clinical monitoring in patients at increased risk as those with polytrauma might allow early detection and therapy of underlying thrombus lesions thus preventing their possible superinfection during Gram-negative bacteremia.

Funding: this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Ethical approval: the present study was approved by the Ethics Committee of the Policlinico Umberto I University Hospital and has therefore been 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 consent requirement was waived due to the anonymized data and the retrospective design of the study.

Conflicts of interest: none

Conflict of interest statement: none

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments: GC, SG, FA, MV participated to patient's clinical management, MS, GC and FA collected clinical data, MS, SG, AR and MV wrote the draft of the manuscript. CB performed statistical analysis. All authors have seen and approved the final version of the manuscript.

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Figure 1. ROC curve about duration of bacteremia >72 hours for development of septic thrombophlebitis

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	-

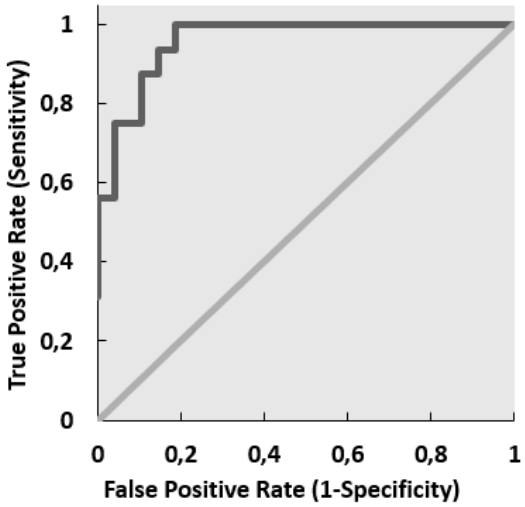
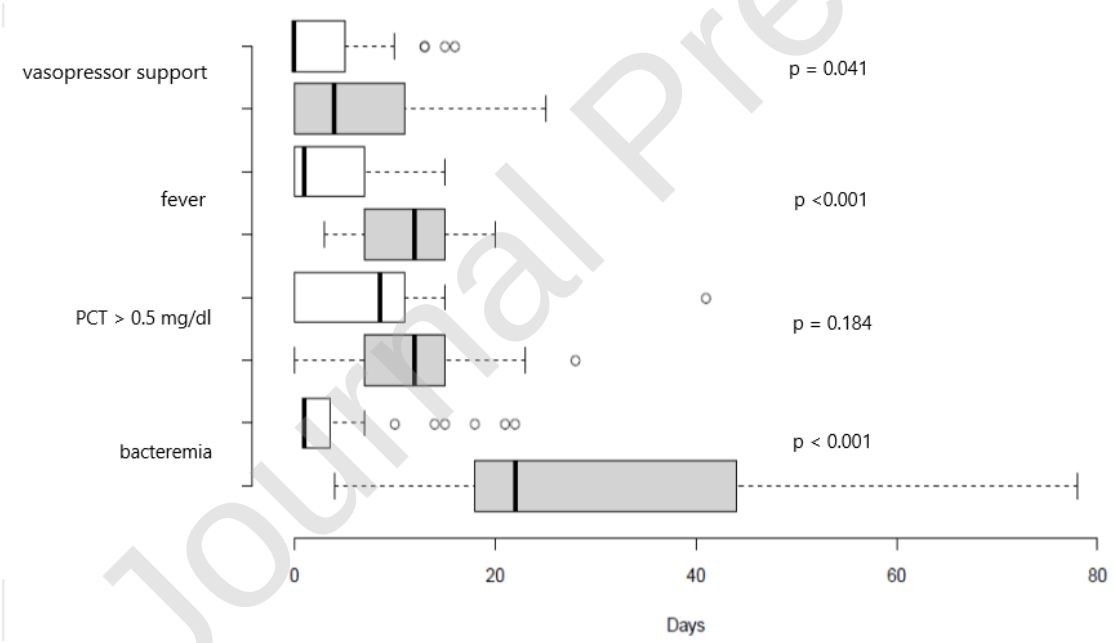


Figure 2. Clinical course of cases (in grey) and controls (in white)



Legend. PCT: procalcitonin.

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Table 1. Description of patients with GN-STP

Sex, age	Cause of ICU admission	Pathogen	Site of GN-STI	Duration of bacteremia (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 pneumonia*	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

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								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

Legend: GN-STP: Gram-negative septic thrombophlebitis; CR: carbapenem-resistant; BSI: bloodstream infection.

Table 2. Site of thrombosis in patients with or 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%)

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Table 3. Univariate analysis about microbiological and clinical features between study groups

	Controls (48)	**Cases (16)**	***P***
Age (years, IQR)	59 (45-74)	53 (40-60)	0.094
Female sex (n, %)	19/48 (40%)	8/16 (50%)	0.243
ICU admission for polytrauma (n, %)	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 (n, %)	28/46 (61%)	5/16 (31%)	**0.018**
SOFA at ICU admission (IQR)	7 (6-10)	9 (7-10)	0.307
Hospitalization within the last 90 days (n, %)	11/44 (25%)	2/16 (13%)	0.050
Antibiotics within the last 30 days (n, %)	36/42 (86%)	14/15 (93%)	0.189
GN infection within the last 30 days (n, %)	18/42 (43%)	1/16 (6%)	**<0.001**
Pitt Bacteremia Score (IQR)	8 (4-8)	7 (6-9)	0.09
Mechanical ventilation (n, %)	35/44 (80%)	14/16 (88%)	0.178
CRRT (n, %)	9/44 (20%)	2/16 (13%)	0.228
Acinetobacter baumannii (n, %)	16/48(33%)	3/16 (19%)	0.111
Klebsiella pneumoniae (n, %)	13/48 (27%)	7/16 (44%)	0.128
Enterobacter spp (n, %)	6/48 (13%)	3/16 (19%)	0.290
Pseudomonas aeruginosa (n, %)	5/48 (10%)	1/16 (6%)	0.296
Escherichia coli (n, %)	3/48 (6%)	0/16 (0%)	0.042
Serratia spp (n, %)	2/48 (4%)	0/16 (0%)	0.080
Morganella morganii (n, %)	1/48 (2%)	1/16 (6%)	0.267
Proteus spp (n, %)	1/48 (2%)	0/16 (0%)	0.161
Providencia spp (n, %)	1/48 (2%)	1/16 (6%)	0.267
MDR isolate (n, %)	29/48 (60%)	9/16 (56%)	0.389
Appropriate empiric therapy (n, %)	24/40 (60%)	7/12 (58%)	0.425
Appropriate definite therapy (n, %)	34/42 (81%)	4/11 (36%)	0.269
Combination antibiotic therapy (n, %)	12/49 (29%)	15/16 (94%)	0.054
Duration of appropriate therapy (days, IQR)	14 (8-16)	22 (14-54)	**0.023**

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Time to PCT normalization (days, IQR)	9 (1-11)	12 (7-15)	0.184
Vasopressor support from FBCs (days, IQR)	0 (0-5)	4 (0-11)	**0.041**
Duration of fever (days, IQR)	1 (0-7)	12 (7-15)	<**0.001**
Days to clinical improvement (days, IQR)	4 (1-11)	15 (12-20)	<**0.001**
Duration of bacteremia (days, IQR)	1 (1-3)	22 (17-45)	<**0.001**
Persistence of bacteremia after clinical improvement (days, IQR)	N/A	14 (0-26)	N/A
7 day mortality (n. %)	10/48 (21%)	0/16 (0%)	<**0.001**
30 day mortality (n, %)	26/39[†] (67%)	3/15[††] (20%)	<**0.001**
60 day mortality (n, %)	28/35*(80%)	5/15[††] (33%)	**0.002**
ICU mortality (n, %)	27/48 (56%)	6/16 (38%)	0.102

Legend. OR: odds ratio; CI: confidence interval; IQR: interquartile range; ICU: intensive care unit; d: days; GN: Gram negative; MDR: multidrug resistant; CRRT: Continuous renal replacement therapy; PCT: procalcitonin; FBCs: first blood cultures; ICU: intensive care unit. N/A: not applicable (clinical improvement occurred before bacteremia clearance).

[†]9 patients lost at follow-up

[††]1 patient lost at follow-up

*13 patients lost at follow-up

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