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Venous thromboembolism is not a risk factor for the development of bloodstream infections in critically ill COVID-19 patients

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Venous thromboembolic complications are common in COVID-19 patients, in particular in critically ill patients [1,2]. Another complication that is frequently observed in COVID-19 patients are bloodstream infections (BSI). BSI in COVID-19 appears to be a particular concern, as the rate of BSI is higher in critically ill patients with COVID-19 compared to non-COVID-19 critically ill patients [3,4]. Given that VTE as well as BSI are common in COVID-19, we hypothesized that venous thromboembolic events are a risk factor for the occurrence of BSI and recurrent and persistent BSI. The clinical consequence would be the need for prolonged duration of antibacterial treatment. Therefore, we performed a retrospective multicenter cohort study in consecutive COVID-19 patients admitted to the ICU, we aimed to study the association between VTE and BSI.

We included all patients (≥18 years old) with PCR confirmed COVID-19 admitted to the intensive care unit (ICU) of the teaching hospital Onze Lieve Vrouwe Gasthuis and two academic Amsterdam UMC hospitals in Amsterdam, the Netherlands, from March 13th to April 30th 2020. Data on clinical status, comorbidities, laboratory values, treatment and outcomes were collected during the first 28 days or until hospital discharge. Formal approval was waived by the Medical Ethics Review Committee of our hospital as the Medical Research Involving Human Subjects Act (WMO) does not apply to this retrospective study.

VTE was defined as pulmonary embolism (PE), deep venous thrombosis (DVT), superficial vein thrombosis or catheter related thrombosis. Ultrasound of the large veins and extremities was performed weekly. The diagnosis of PE was based on computed tomography (CT) imaging, which was performed on clinical and/or biomarker suspicion [5]. All patients received thrombosis prophylaxis with nadroparin 2850 IU to 5700 IU daily depending on weight.

For the diagnosis of BSI, at least one positive blood culture was required for presence of anaerobic, enterococci or gram-negative bacteria. At least two positive blood cultures with identical microorganisms were needed for the diagnosis of a CNS bacteremia, to reduce the chance of contamination [6]. Blood cultures were taken if patients had fever

Abbreviations: BSI, bloodstream infections; CNS, coagulase negative staphylococci; COVID-19, coronavirus disease 2019; CT, computed tomography; DVT, deep venous thrombosis; ICU, intensive care units; LOS, length of stay; PE, pulmonary embolism; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SDD, selective decontamination of the digestive tract; VTE, venous thromboembolism.

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(temperature > 38.5 °C). In case of a positive blood culture, all central venous catheters were removed and if indicated, replaced. Recurrent bacteremia was defined as a second episode of bacteremia with the same pathogen and a similar resistance pattern occurring after treatment with antibiotics for at least 48 h and at least one negative blood culture in between the initial and latest positive test result. Persistent bacteremia was confirmed if a blood culture remained positive after at least 48 h of adequate antibiotic treatment. All patients received selective decontamination of the digestive tract (SDD) consisting of cefotaxime iv. during the first three days of ICU admission and topical antibiotics in the digestive tract. Other COVID-19 treatment was supportive, as data collection occurred prior to trials reporting effects of steroids and tocilizumab.

Data is presented as mean with standard deviation or median with interquartile ranges according to normality, difference between groups was analyzed with either the Student *t*-test or Mann-Whitney *U* test. Categorical data are presented as percentage, difference between groups was analyzed with Pearson's chi-square test. Statistical significance was set at $P < 0.05$. The determination of VTE as a risk factor for the development of BSI required multiple steps. First, to correct for the pre-test likelihood of developing a VTE, a propensity score was calculated. To do this, potential risk factors for VTE were identified. Multiple variables were selected and tested for significant differences between patients who did and did not develop VTE. Factors with a significance level of $P < 0.10$ were included as potential predictors in the logistic regression model for calculation of the propensity score. The following factors were selected with backward Wald's selection of variables and included in the propensity score: SOFA score at day 8, mechanical ventilation, CRP at day 8, ICU length of stay and immunotherapy. Second, a fixed regression model with BSI as independent variable and VTE as a determinant with the final propensity score included as a covariate was used to assess whether VTE is a risk factor for BSI. Significance levels were shown to denote the power of its association. Statistical analysis was performed with SPSS© version 26.0. (IBM©, New York, New York, the United states).

In total, 188 ICU patients were included, of whom 55 (29.3%) developed a BSI. Patients who developed a BSI had greater disease severity, longer duration of mechanical ventilation and longer ICU length of stay compared to those not developing BSI. CNS and Enterococcal species were the organisms most frequently found, in 43 (78.2%) and 30 (54.5%) patients respectively. In nearly half of the patients with BSI, multiple pathogens were cultured. Gram-negative pathogens and candida species were not identified.

Of 188 patients, 81 (43%) developed a VTE, Table 1 shows the uncorrected differences in parameters between patients with and without VTE. The median time to develop VTE was 8 days after ICU admission. Patients who had a VTE were sicker and had a longer ICU length of stay than patients without VTE.

The total amount of bacteremias as well as persistent bacteremias was proportionally higher in patients with VTE. Of the patients with VTE, 35 (43.2%) developed a BSI, 7 (8.6%) developed recurrent BSI and 12 (14.8%) persistent BSI. In the patients with both BSI and VTE, pulmonary embolism occurred in 21 patients, deep venous thrombosis in 11 patients and superficial vein thrombosis or catheter related thrombosis in only 3 patients. The median time to develop BSI in patients with VTE was 10 days. Hence, to determine whether VTE was independently associated with BSI, the propensity score was calculated to correct for the a-priori likelihood of patients developing a VTE. Risk factors in Table 1 with a *P*-value <0.10 were included in the model to calculate the propensity score (Table 2).

After correction for the propensity score, VTE ceased to be significantly associated with BSI (Table 2), indicating that confounding variables of disease severity were responsible for the apparent increased prevalence of BSI in COVID-19 patients with VTE.

In critically ill COVID-19 patients, the incidence of BSI as well as persistent BSI, was higher in patients with VTE than in those without VTE. However, this association disappeared when correcting for confounding variables of disease severity. Thereby, the risk of BSI in COVID-19 appears to not be driven by the presence of thrombotic complications.

We found a high incidence of CNS, Enterococci and mixed bloodstream infections. These pathogens may suggest that COVID-19 results in bacterial translocation from the gut, due to invasion of the virus into the gut mucosa or possibly due to shock-induced hyper-permeability of the gut barrier [7]. However, we did not observe any anaerobic BSI which would be expected in BSI originating from the gut. The absence of gram-negative BSI is presumably explained by the use of SDD.

An alternative explanation for the high incidence could be BSI originating from the skin [8,9]. Possibly, working in a cohort and deployment of nurses not regularly working in the ICU reduced adherence to standard measures to prevent catheter related BSI. However, the increased incidence of BSI we found cannot exclusively be explained by skin contamination, as a substantial proportion of all BSI found in our research population was caused by enterococcal species, which are typically found in the gut.

The high incidence of both BSI and VTE in critically ill COVID-19 patients appears to be the result of increased disease severity. In accordance with this, patients with BSI spent more time on the ICU than patients without a BSI. Although we corrected for ICU length of stay in the propensity score, attrition bias cannot be ruled out. Another limitation of this study is the retrospective design. A strength of our study is its external validity for other centers, given that data was collected from both academic and non-academic hospitals.

Our findings have relevance. The high incidence of (recurrent) BSI frequently prompted discussions at our institutions about a possible

Table 1
Characteristics of critically ill COVID-19 patients with and without venous thromboembolism (VTE).

	VTE $N = 81$	No VTE $N = 107$	*P* value
Age (yrs, mean, SD)	61.3 (10.5)	61.3 (11.7)	0.970
Sex (male, n, %)	64 (79)	81 (75.7)	0.673
BMI (mean, SD)	27.7 (4.4)	28.9 (5.3)	0.111
Immunosuppressive therapy (n, %)	3 (3.7)	7 (6.5)	0.475
SOFA score day 8 (median, IQR)	7 (5–9)	4 (0–7)	<0.001
Mechanical ventilation (n, %)	80 (98.8)	84 (78.5)	<0.001
C-reactive protein on day 8 (g/dl, mean, SD)	164 (72–256)	53 (15–113)	<0.001
Bloodstream infections (n, %)	35 (43.2)	20 (18.7)	<0.001
Persistent bacteremia (n, %)	12 (14.8)	2 (1.9)	0.001
Recurrent bacteremia (n, %)	7 (8.6)	3 (2.8)	0.073
Days on ICU until onset bacteremia (median, IQR)	10 (3–15)	7 (3−12)	0.357
LOS ICU (median, IQR)	14 (8–19)	8 (5–12)	<0.001
Mortality day 28 (n, %)	21 (25.9)	29 (27.1)	0.940

BMI, body mass index. SOFA, sequential organ failure assessment. LOS ICU, length of stay in the intensive care unit. VTE, venous thromboembolism.

Table 2
Venous thromboembolism as a risk factor for bloodstream infection.

Variables in propensity score	Regression coefficient		*P* value
CRP on day 8	0.007		0.027
ICU LOS	0.157		0.043
Variables in final model	Odds ratio	95% CI	
Propensity score	–	–	0.002
VTE	2.283	0.741–7.022	0.15

Variables entered for the final association model were: SOFA at day 8, mechanical ventilation, CRP at day 8, ICU LOS and immunosuppressive therapy. Regression coefficient is the value given by logistic regression to depict the weight of the variables in the propensity score.
Odds ratios of the propensity score are not presented as it is not a true odds (134, (6.365–2836.14)).

benefit of prolonged treatment with vancomycin, in particular in patients with a prolonged disease course or persistent fever. These results do not underline such an approach.

To conclude, both BSI with gram positive bacteria and VTE are common findings in critically ill COVID-19 patients, but VTE is not associated with BSI. A standard need for prolonged duration of antibacterial treatment is not justified.

Author contributions

All authors contributed substantially to the study design and interpretation of the data. R.W.G. Dujardin, B.N. Hilderink and W.E. Haksteen collected data from electronical patient records. B.N. Hilderink and W.E. Haksteen analyzed the data. The first and final version of the manuscript was written by W.E. Haksteen, B.N. Hilderink, M.C.A. Müller and N.P. Juffermans. All authors revised the manuscript critically and approved the final version.

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Declaration of competing interest

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.

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