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Low-grade endotoxemia is associated with cardiovascular events in community-acquired pneumonia

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SUMMARY

Objectives: Community-acquired pneumonia (CAP) is associated with low-grade endotoxemia but its relationship with cardiovascular events (CVE) has not been investigated.
Methods: We evaluated the incidence of CVE including myocardial infarction, stroke, and cardiovascular death in 523 adult patients hospitalized for CAP. Serum lipopolysaccharide (LPS) and zonulin, a marker of gut permeability, were analyzed in the cohort, that was followed-up during hospitalization and up to 43 months thereafter.
Results: During the hospital-stay, 55 patients experienced CVE with a progressive increase from the lowest (0.6%) to highest LPS tertile (23.6%, $p < 0.001$). Logistic regression analyses showed that higher LPS tertile was independently associated with CVE; LPS significantly correlated with age, hs-CRP and zonulin. In a subgroup of 23 CAP patients, blood *E. coli* DNA was higher in patients compared to 24 controls and correlated with LPS. During the long-term follow-up, 102 new CVE were registered; the highest tertile of LPS levels was associated with incident CVE; Cox regression analysis showed that LPS tertiles, age, history of CHD, and diabetes independently predicted CVE.
Conclusions: In CAP low-grade endotoxemia is associated to short- and long-term risk of CVE. Further study is necessary to assess if lowering LPS by non-absorbable antibiotics may result in improved outcomes.
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Introduction

There is an increasing body of evidence that patients with pulmonary infection may experience cardiovascular events (CVE) during the acute phase of the disease. Patients with community-acquired pneumonia (CAP) may suffer from myocardial cardiac infarction, stroke and cardiovascular death with an incidence of roughly 10% within one month from hospitalization depending on the disease severity.[1,2] The strong association between pneumonia and CVE has been recently strengthened in patients with Covid-19, in whom an even more elevated risk of CVE compared to CAP was detected.[3] The mechanism accounting for the occurrence of CVE has not been fully elucidated. Patients with CAP display a prothrombotic state documented by enhanced platelet activation and thrombin generation with an association with intrahospital CVE but it is unclear if specific pathogen or the accompanying systemic inflammation may be responsible for the prothrombotic state.[4–6] We recently reported that CAP may be complicated by enhanced gut permeability, that is responsible for lipopolysaccharide (LPS) translocation into systemic circulation suggesting that gut dysbiosis may be implicated in low-grade endotoxemia.[6,7] Thus, CAP patients display enhanced blood levels of zonulin,[7] that is an indirect marker of gut permeability as upon activation zonulin increases gut permeability by disassembling the intestinal tight junctions.[8]

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LPS is a glycolipid of intestinal Gram-negative bacteria, that circulates in healthy subjects at very low concentrations, i.e., 20 ng/ml[9]; its increase reflects changes in gut barrier functionality and may result in deleterious effects for its intrinsic pro-inflammatory and prothrombotic properties.[9] Regarding this last point, LPS may act at level of several cell lines, such as endothelial cells, macrophages and platelet to elicit an ongoing prothrombotic state so facilitating thrombus growth[10]; experimental model mimicking low-grade endotoxemia showed, in fact, that LPS enhances thrombus growth via interaction with its receptor Toll-like receptor 4 (TLR4).[11] Thus, the potential relationship between LPS and thrombosis prompted us to evaluate if LPS is associated with CVE in a cohort of patients hospitalized for CAP and followed-up until discharge and during a long-term follow-up.

Methods

CAP patients

We analyzed data from a prospective observational study aimed to evaluate the incidence of major vascular events in hospitalized adult patients with CAP (clinical.trial.gov: NCT01773863).[4,12]

This cohort study prospectively recruited and followed-up patients referred to 3 medical centers from the University-Hospital Policlinico Umberto I, Sapienza University of Rome, Italy: Department of Internal Medicine and Medical Specialties, Department of Clinical Medicine, Department of Public Health and Infectious Diseases.

We enrolled adults who met the following criteria: 1) age ≥18 years; 2) clinical presentation of an acute illness with at least two or more of the signs or symptoms of CAP, as previously reported 4 and 3) presence of new consolidation(s) on chest X-ray or CT-scan. Pneumonia was defined as CAP diagnosed upon hospitalization in a patient who did not meet the criteria for healthcare-associated pneumonia.[13]

Exclusion criteria were: immunosuppression (HIV infection, chemotherapy, high dose of immunosuppressive agents to prevent the rejection of transplanted organs and tissues or to treat autoimmune diseases); critical illness requiring admission to an intensive care unit,[15] presence of malignancy; pregnancy or breastfeeding; documented severe allergy to antibiotics; healthcare-associated pneumonia.

All patients with CAP admitted to the 3 units after giving written informed consent from October 2011 to January 2018, were prospectively recruited and followed up. The present study was conducted according to the principles stated in the Declaration of Helsinki. The study was approved by the local Ethics Committee Prot. n. 864/11.

Baseline assessment

Data regarding demographic characteristics, comorbidities, and concurrent therapy were collected after inclusion in the study. The severity of CAP was estimated by the Pneumonia Severity Index (PSI), a validated prediction score for 30-day mortality in patients with CAP.[14] For each patient recruited, 12-lead electrocardiogram (ECG) and routine blood laboratory tests were immediately performed after admission. Hs-cTnT were measured at baseline and every 24 h up to 3 days from admission and at hospital dismission.

Pre-existence of type 2 diabetes mellitus (T2DM), hypertension, coronary heart disease (CHD), dyslipidemia, peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), heart failure (HF), chronic (persistent or permanent) atrial fibrillation (CAF) and paroxysmal atrial fibrillation (PAF) were defined as previously described.[15]

In-hospital outcomes

Study endpoints included CVE such as myocardial infarction (MI), ischemic stroke and cardiovascular death. MI was diagnosed according to the Fourth Universal Definition of Myocardial Infarction.[16] ST-elevation MI (STEMI) and non-ST-elevation MI (NSTEMI) were defined as previously reported[16] and were confirmed by cardiologists. Ischemic stroke was defined as previously reported[17] and documented by neuroimaging evaluation (brain MRI, or if not possible, brain CT).

Cardiovascular death included: fatal MI; fatal stroke; sudden death; death due to cardiogenic shock in patients with HF; pulmonary embolism, rupture or dissection of aneurysm, death related to cardiovascular investigation/procedure/operation; death due to other specified cardiovascular causes.

In hospital death for non-cardiovascular causes were considered as a censoring event.

Long-term follow-up

CVE registered during the follow-up were obtained by review of hospital databases, medical records, death certificates or telephone interviews. Adjudication of the events was performed by a central adjudication committee (CC and SM) who did not participate in the patients' recruitment and follow-up and was unaware of the clinical and laboratory characteristics of any patient.

Censored cases included: patients who refused to participate to the follow-up interviews after hospital dismission, patients who stopped to answer to telephone calls or refused telephone interviews during the follow-up, patients who died for non-cardiovascular causes.

Mortality including also non-cardiovascular death during the follow-up was registered.

LPS and Zonulin measurement

LPS serum levels were measured by a commercial ELISA method (Cusabio). Values were expressed as pg/ml; intra-assay and inter-assay coefficients of variation were 8% and 10%, respectively.

Zonulin serum measurement was performed by ELISA Kit (Elabscience). Antibody specific for Zonulin has been pre-coated onto a microplate and 100 μL of standards and patient sera samples were added and incubated 90 min at 37 °C. Then a biotinylated detection antibody specific for Zonulin and Avidin-Horseradish Peroxidase (HRP) conjugate is added. The amount of Zonulin was measured with a microplate auto-reader at 450 nm. Values were expressed as ng/ml; coefficients of variation were < 10%.

E. coli DNA analysis

DNA was extracted from 200 μL serum by QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) following the manufacturer's instruction. DNA was eluted with 100 μL of 70° preheated water. The yield and purity of DNA were measured by reading A260 and A260/A280 using Nanodrop (ThermoFisher, US). A Real-time PCR reaction for specific amplification of a 3 V hypervariable region of the 16 S ribosomal RNA gene of *Escherichia coli* was developed. 20 ng of total DNA were added into a reaction mix containing SYBR Green PCR Master Mix (ThermoFisher, US), 500 nM primer forward (CCAGACTCCTACGGGAGGCAG), and 500 nM reverse primer (CGTATTACCGCGGCTGCTG) to complete a final volume of 20 μL. Internal control was performed for each sample by beta-globin amplification using the following primers: forward (ACACAACTGTGTTCACTAGC), and reverse (GAAACCCAAGAGTCTTCTCT). To quantify *E. coli* DNA a standard curve was generated using a dilution series of 5 concentrations of *E. coli* purified genomic DNA. Data were expressed as pg/20 ng of DNA).

E. coli DNA was analyzed in 23 randomly chosen CAP patients in serum collected at hospital admission and in 24 controls matched for age, sex, and comorbidities. Control subjects were selected among outpatients referring to the Day Service of Internal Medicine of the Department of Internal Medicine and Medical Specialties, Sapienza University Hospital.

Statistical analysis

Categorical variables are reported as counts and percentages and continuous variables as mean ± standard deviation (SD), or medians and interquartile ranges (IQRs). Differences between percentages were assessed by chi-square or Fisher exact tests. All continuous variables were tested for normality with the Shapiro-Wilk test. Student unpaired t-tests were used for normally distributed continuous variables. Appropriate nonparametric tests (Mann-Whitney, Wilcoxon, and Spearman rank correlation tests) were used for the other variables. The bivariate and multivariate effects of prognostic factors on thrombotic events were assessed by means of logistic regression models. Wald confidence intervals and tests for odds ratios (O.R.) and adjusted O.R. were computed based on the estimated standard errors. Survival curves were estimated using the Kaplan-Meier product-limit estimator and compared using the log-rank test. Cox proportional hazards analysis was used to calculate the adjusted hazard ratios (H.R.) and 95% confidence interval (CI) for each clinical variable. Only p values <0.05 were considered statistically significant. All tests were 2-tailed, and analyses were performed using computer software packages (IBM SPSS Statistics 25).

Results

LPS and in-hospital cardiovascular events

We recruited 523 patients hospitalized for CAP (329 males; 194 females; age: 71.45 ± 16.1 years). Most of the patients had arterial hypertension (69%). A history of CHD was present in 29% of patients, previous stroke in 11%, T2DM in 25%, COPD in 31%, PAD in 6%, and dyslipidemia in 25%. A history of PAF in 12% of patients, while 14% were affected by CAF, and 18% had chronic kidney disease (Table 1).

The median hospital length was 10 [7–13] days. During the hospital-stay, 55 patients experienced a CVE: 45 MI (43 NSTEMI AND 2 STEMI) and 10 strokes.

Patients who experienced a CVE were older, and more likely to have hypertension, history of CHD, T2DM and heart failure heart failure than CVE-free patients. Also, patients who experienced CVE were more likely to have a higher PSI score and belonged to higher PSI classes than CVE-free patients. LPS serum levels significantly decreased at discharge compared to the values registered at admission (55 [38–74] vs 133 [98–196] ng/ml; $p < 0.001$). LPS levels were higher in patients who experienced CVE than CVE-free patients at hospital admission (194 [176–351] vs. 124 [92–188], $p < 0.001$) as well as at hospital discharge (73 [63–88] vs. 53 [37–70] ng/ml; $p < 0.01$) (Fig. 1A).

After dividing LPS according to tertiles, a progressive increasing number of CVE during hospitalization was found (from 0.6% in the lowest to 23.6% in the highest, $p < 0.001$) (Fig. 1B). Logistic regression analyses showed that higher LPS tertile was independently associated with an increased risk of CVE, after adjusting for age, comorbidities, and PSI classes (Table 2).

Variables associated with LPS serum levels

At hospital admission LPS showed a correlation with age ($Rs = 0.121$; $p = 0.006$) and hs-CRP (0.195; $p < 0.001$). Logistic univariate analyses showed that the highest LPS tertile was directly associated with age, CHD, history of stroke/TIA, COPD, paroxysmal atrial fibrillation, heart failure, PSI, and hs-CPR, and inversely, with the use of high intensity statins, i.e., atorvastatin 40–80 mg daily or rosuvastatin 20–40 mg daily.[18] A trend for a direct correlation was also found for chronic kidney disease and T2DM (Table 3). A logistic multivariate regression analysis showed that age, history of stroke/TIA, COPD, HF and higher hs-CRP levels remained directly associated, while high intensity statins remained inversely associated to the highest tertile (Table 4).

Zonulin serum levels were analyzed in the last 257 consecutively recruited CAP patients. Clinical characteristics of this subgroup of patients are described in Supplemental Table S1. Like LPS serum levels, zonulin levels were higher at admission compared to discharge: (3.2 [2.0–4.2] vs. 2.4 [1.6–3]; $p < 0.001$). LPS correlated with zonulin levels both at admission ($Rs = 0.393$; $p < 0.001$), and at discharge ($Rs = 0.317$; $p < 0.001$).

Finally, in 23 randomly chosen CAP patients and in 24 controls, blood *E. coli* DNA was measured. Clinical characteristics of CAP and controls are reported in Supplemental Table S2. Compared to controls, blood *E. coli* DNA was higher in CAP patients (67 [47–110] pg/20 ng of DNA vs. 41 [34–81] pg/20 ng of DNA, $p = 0.032$). Also, *E. coli* DNA correlated with LPS serum levels ($Rs = 0.536$; $p = 0.008$) and PSI score ($Rs = 0.468$; $p = 0.024$).

LPS, cardiovascular events and mortality at long-term follow-up

After hospitalization, patients were followed-up for a median of 43 [20–60] months, yielding 21,654 month-persons of follow-up. During the long-term follow-up, 102 new CVEs were reported: 32 non-fatal MI, 10 non-fatal strokes, 60 cardiovascular deaths. The highest tertile of baseline LPS levels was associated with increased risk of developing CVE during the follow-up (Fig. 1C). Cox regression analysis showed that higher LPS tertile, age, history of CHD, and T2DM independently predicted CVE after adjusting for PSI, sex, and comorbidities (Supplemental Table S3). Overall, 134 patients died during the follow-up (64 for non-cardiovascular causes). The highest tertile of baseline LPS levels was associated with all-cause mortality during the follow-up (Fig. 1D). Cox regression analysis showed that the highest LPS tertile, age, and T2DM independently predicted mortality after adjusting for PSI, sex, and comorbidities (Supplemental Table S4).

Discussion

The study provides evidence that in patients with CAP elevated levels of LPS are predictive of CVE during the hospital stay as well as a follow-up of about 3 years.

Previous studies in general population or in patients at risk of CVE demonstrated an association between low-grade endotoxemia and CVE.[9] Low-grade endotoxemia is associated with enhanced blood levels of LPS, which are, however, two-fold lower than the LPS concentrations detected in sepsis.[9] Several factors may contribute to low-grade endotoxemia such as metabolic disease, alcohol abuse, systemic inflammation and infections; all these factors may elicit alteration of gut microbiota resulting in intestinal barrier dysfunction with ensuing translocation of bacteria or bacteria products into systemic circulation.[9]

Acute infections are also associated with low-grade endotoxemia as shown in a cohort of Covid-19 and CAP patients suggesting the infection/inflammation may contribute to translocation of bacteria products into systemic circulation.[6,19] This hypothesis is further supported by the present study showing that serum LPS and serum zonulin, that is an indirect marker of gut barrier dysfunction,[8] are significantly correlated suggesting that low-grade endotoxemia may be related to gut barrier dysfunction. To support this hypothesis in a small group of CAP patients we examined the concentration of *E. coli*, that is a Gram-negative bacteria hosted in the gastrointestinal tube; the study showed a higher concentration of *E. coli* in CAP patients

Table 1
CAP patient characteristics.

	All	CAP without intra-hospital CVE	CAP with intra-hospital CVE	p Value
N	523	468	55	
Age (years)	71.5 ± 16.1	70.5 ± 16.4	80.3 ± 9.5	< 0.001
Sex (males)	63%	63%	65%	0.679
Smoking habit	21%	21%	16%	0.406
BMI (kg/m^2)	26.0 ± 3.7	25.9 ± 3.7	26.6 ± 3.6	0.148
Preexisting comorbid conditions				
• History of CHD (%)	29	26	54	< 0.001
• Previous stroke (%)	11	9	22	0.004
• T2DM (%)	25	23	36	0.037
• Hypertension (%)	69	68	84	0.015
• CKD (%)	18	17	25	0.306
• COPD (%)	31	31	33	0.766
• Heart failure (%)	17	15	40	< 0.001
• PAF (%)	12	12	18	0.172
• CAF (%)	14	13	18	0.315
• Peripheral artery disease (%)	6	6	9	0.370
• Dyslipidemia (%)	25	25	32	0.286
Aspirin (%)	32	32	38	0.323
P2Y12-inhibitors (%)	12	12	14	0.622
Low-moderate intensity statins (%)	23	23	34	0.041
High intensity statins (%)	7	7	5	0.685
Heparins (%)	6	5	11	0.079
Oral anticoagulants (%)	14	14	16	0.610
hs-CRP (ng/ml)*	48 [23.0–119]	46 [23–121]	56 [30–98]	0.530
LPS (ng/ml)*	133 [98–196]	124 [92–188]	194 [176–351]	< 0.001
PSI score*	90 [70–116]	87 [69–112]	117 [97–137]	< 0.001
PSI class II (%)	27	30	4	
PSI class III (%)	24	25	16	< 0.001
PSI class IV (%)	36	35	47	
PSI class V (%)	13	10	33	

BMI = body mass index; CAF = chronic (persistent or permanent) atrial fibrillation; COPD = chronic obstructive pulmonary disease; CHD = coronary heart disease; CKD = chronic kidney disease; hs-CRP = high-sensitivity C-reactive protein; LPS = Lipopolysaccharides; PAF = paroxysmal atrial fibrillation; PSI = pneumonia severity index; T2DM = type 2 diabetes mellitus.

* Data are expressed as medians (interquartile ranges).

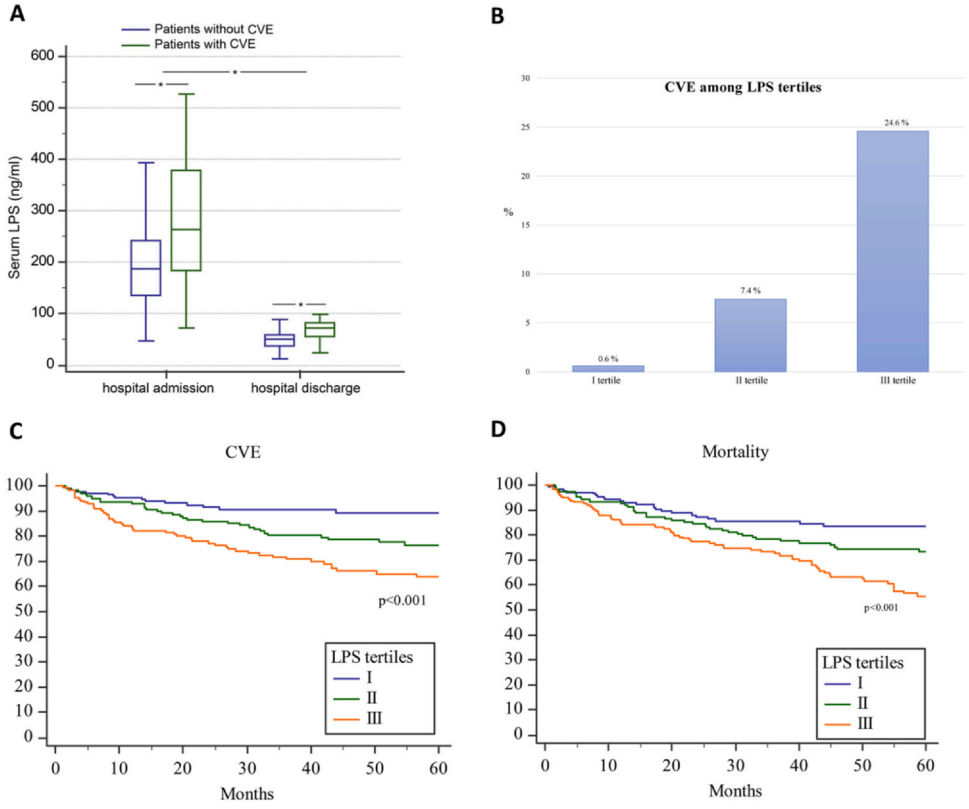

Fig. 1. (A) LPS levels at admission and at hospital discharge in patients who experienced or not CVE during the in-hospital stay (*p < 0.001). (B) Percentage of in-hospital CVE according to baseline LPS tertiles. (C) Kaplan–Meier estimates of time to CVE according to LPS tertiles during the long-term follow-up. (D) Kaplan–Meier estimates of time to mortality according to LPS tertiles during the long-term follow-up.

Table 2
Logistic regression analyses: Predictors of in hospital CVEs.

	O.R:	95% CI		p Value
Model A				
LPS tertiles*	4.299	2.493	7.412	< 0.001
Age	1.058	1.024	1.093	< 0.001
Heart failure	2.272	1.144	4.514	0.019
History of CHD	2.272	1.144	4.514	0.049
Model B				
LPS tertiles*	4.803	2.755	8.373	< 0.001
History of CHD	2.267	1.202	4.277	0.012
PSI classes**	2.569	1.732	3.809	< 0.001

CHD = coronary heart disease; LPS = Lipopolysaccharides; PSI = Pneumonia Severity Index.
Model A included LPS tertiles, age, heart failure, history of CHD, hypertension, previous stroke, and diabetes.
Model B: same variables included in the Model A plus PSI classes.
* For each increasing tertiles.
** For each increasing classes.

Table 3
Univariate logistic regression analyses: Variables associated with the highest LPS tertile.

Variable	O.R.	95% CI		p Value
Age	1.017	1.005	1.030	0.005
Sex (male vs. female)	1.017	0.698	1.482	0.930
BMI	0.998	0.967	1.031	0.912
Smoking habit	1.234	0.793	1.918	0.351
History of CHD	1.617	1.092	2.395	0.016
History of stroke	1.966	1.107	3.491	0.021
T2DM	1.617	1.092	2.395	0.097
Dyslipidemia	0.728	0.466	1.135	0.161
Hypertension	1.350	0.901	2.023	0.146
CKD	1.542	.956	2.487	0.076
COPD	1.542	.956	2.487	0.003
Heart failure	1.948	1.230	3.086	0.005
PAF	1.743	1.022	2.974	0.041
CAF	1.016	0.592	1.743	0.995
PAD	0.864	0.402	1.859	0.709
hs-CRP (ng/ml)	1.470	1.249	1.730	< 0.001
Aspirin	1.281	0.864	1.899	0.218
P2Y12-inhibitors	1.465	0.849	2.528	0.170
High intensity statins	2.267	1.202	4.277	0.012
Heparins	1.045	0.471	2.318	0.913
Oral anticoagulants	0.796	0.459	1.380	0.416
PSI classes	1.234	1.028	1.481	0.024

BMI = body mass index; CAF = chronic (persistent or permanent) atrial fibrillation; CHD = coronary heart disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease. hs-CRP = high-sensitivity C-reactive protein; PAD = peripheral artery disease; PAF = paroxysmal atrial fibrillation; PSI = Pneumonia Severity Index; T2DM = type 2 diabetes mellitus.

Table 4
Multivariate logistic regression analysis: Variables independently associated with the highest LPS tertile.

Variable	O.R.	95% CI		p Value
Age	1.014	1.001	1.028	0.049
History of stroke	1.960	1.035	3.713	0.039
COPD	1.636	1.064	2.517	0.025
Heart failure	2.134	1.277	3.566	0.004
hs-CRP (ng/ml)	1.533	1.291	1.821	< 0.001
High intensity statins	0.245	0.089	0.675	0.007

COPD = chronic obstructive pulmonary disease; hs-CRP = high-sensitivity C-reactive protein.

compared to controls with a significant correlation between the *E. coli* concentration and LPS serum levels suggesting a potentially prominent role of *E. coli* in LPS blood elevation. It is interesting to underline at this regard the presence of *E. coli* also in patients without infections, that is agreement with a previous study showing the bacteria or bacteria products may be detected in apparently healthy subjects[11]; in this specific case the presence of *E. coli* may be explained by the fact that our controls had atherosclerotic risk factors that may be associated with low-grade endotoxemia.[9]

The novelty of the present study is in the analysis of the impact of low-grade endotoxemia versus CVE in patients with acute infections. Thus, to best of our knowledge, this is the first study reporting the relationship between low-grade endotoxemia and CVE in short- and long-term follow-up in a population with CAP. Patients experiencing CVE during the hospital stay had higher LPS values compared with patients without CVE and patients in the highest LPS tertile, i.e., 194 pg/ml serum LPS, had more probability of experiencing CVE. Such association was independent from other established factors of CVE and overall, from PSI, that has been already reported as independent predictor of CVE.[2]

The association between LPS and CVE was also confirmed in a long-term follow-up where the highest LPS tertile was associated with CVE and mortality along with age, and diabetes after adjusting for PSI, sex, and comorbidities. The relationship between LPS and CVE is biologically plausible as LPS, at concentration detectable in peripheral blood of CAP patients, may amplify the platelet response to common agonizts by up-regulating Nox2, the most important cellular producer of reactive oxidant species,[20] and elicit release of clotting factors such as Factor VIII and von Willebrand Factor by endothelial cells.[21] Also, in animal injected with small amount of LPS, an enhanced platelet activation was detected while combination of LPS with a TLR4 inhibitor blunted this effect.[10]

The study has limitations and implications. The study has been conducted in a single hospital and included only Caucasian population, therefore multicenter study including larger number of patients of different race is necessary to confirm the present data. We used serum zonulin as indirect marker of gut permeability,[8] thereby further study with methodology directly exploring gut permeability should be done to support our findings. Blood LPS was measured only during hospitalization therefore we are not aware if increase of LPS could persist for long-term after the acute phase. The mechanism accounting for enhanced gut permeability was not fully investigated. Logistic multivariate regression analysis showed that higher hs-CRP levels remained directly associated with highest LPS tertile suggesting a potential bidirectional interplay between LPS and inflammation; inflammation, may, in fact, increase gut permeability so favoring translocation of LPS into systemic circulation, that, in turn, may exacerbate inflammation via interaction with its receptor TLR4.[9] The relationship between LPS circulating levels and inflammation was further corroborated by the significant decrease of LPS at patients' discharge compared to the values detected at hospital admission. It is, therefore, to clarify if acute infection per se causes gut dysbiosis-related endotoxemia or if systemic inflammation may play also a role as indicated by the ability of inflammatory cytokines such as Tumor Necrosis Factor alpha to downregulate intestinal adhesive proteins so increasing gut permeability.[9] In this context we cannot exclude that other factors such as coexistent bacteremia could also influence long-term poor outcomes.[22] The relationship between LPS and CVE may be dependent upon the procoagulant activity exerted by LPS; thus in a previous study we showed a significant association between serum LPS and in vivo thrombin generation.[6] Also, experimental in vivo study showed that low- grade endotoxemia enhances thrombus growth via TLR4.[11] The association between LPS and CVE could suggest the potential usefulness of non-absorbable antibiotics to lower LPS-related inflammation and eventually CVE; in this context it worthwhile to report the ability of the non-absorbable antibiotic rifaximin to lower blood LPS in patients with low-grade endotoxemia.[9]

Finally, we found that patients given high-dose statins had lower LPS levels, that may explained by the fact that statins are capable of up-regulating the adhesive intestinal proteins in vitro so improving gut barrier dysfunction.[9] Further ad hoc study is necessary to

evaluate if this effect may be recapitulate in vivo and, thereby, if statins may be useful for the treatment of gut dysbiosis-related low-grade endotoxemia.

In conclusion, CAP is characterized by elevated levels of LPS, that are associated with a short- and long-term risk of CVE and mortality. Further study is necessary to assess if lowering LPS by non-absorbable oral antibiotics may result in improved outcome.

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Authors contributions

R Cangemi and R Carnevale were responsible for design of the study, data interpretation, interpreting results, writing the manuscript, updating reference lists, and creating the table and figures. CN, SB, and VP were responsible for analyzing data, interpreting results, and making the table and figure. CC, GF, and PP participated in interpreting the results and writing the manuscript. VF was responsible for study conception, writing the manuscript, conducting the study, interpreting results, and approbation the final version for submission.

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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None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2023.11.010.

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