[Original Research]

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Rate and Predictors of Bacteremia in Afebrile Community-Acquired Pneumonia

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BACKGROUND: Although blood cultures (BCs) are the criterion standard for detecting bacteremia, the utility of BCs in patients with community-acquired pneumonia (CAP) is controversial. This study describes the proportion of patients with CAP and afebrile bacteremia and identifies the clinical characteristics predicting the necessity for BCs in patients who are afebrile.

METHODS: Bacteremia rates were determined in 4,349 patients with CAP enrolled in the multinational cohort study CAPNETZ and stratified by presence of fever at first patient contact. Independent predictors of bacteremia in patients who were afebrile were determined retrospectively using logistic regression analysis.

RESULTS: Bacteremic pneumonia was present in 190 of 2,116 patients who were febrile (8.9%), 101 of 2,149 patients who were not afebrile (4.7%), and one of 23 patients with hypothermia (4.3%). Bacteremia rates increased with the CURB-65 score from 3.5% in patients with CURB-65 score of 0 to 17.1% in patients with CURB-65 score of 4. Patients with afebrile bacteremia exhibited the highest 28-day mortality rate (9.9%). Positive pneumococcal urinary antigen test (adjusted OR [AOR], 4.6; 95% CI, 2.6-8.2), C-reactive protein level > 200 mg/L (AOR, 3.1; 95% CI, 1.9-5.2), and BUN level ≥ 30 mg/dL (AOR, 3.1; 95% CI, 1.9-5.3) were independent positive predictors, and antibiotic pretreatment (AOR, 0.3; 95% CI, 0.1-0.6) was an independent negative predictor of bacteremia in patients who were afebrile.

CONCLUSIONS: A relevant proportion of patients with bacteremic CAP were afebrile. These patients had an increased mortality rate compared with patients with febrile bacteremia or nonbacteremic pneumonia. Therefore, the relevance of fever as an indicator for BC necessity merits reconsideration.

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KEY WORDS: bacteremia; community-acquired pneumonia (CAP); fever; predictor

ABBREVIATIONS: AOR = adjusted OR; BC = blood culture; CAP = community-acquired pneumonia; CRP = C-reactive protein

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With an estimated annual incidence of 400,000 to 680,000 cases per year in Germany,[1] community-acquired pneumonia (CAP) is currently the leading infection-related cause of death in Germany (https://www.destatis.de). It results in more hospitalizations than those caused by heart attack or stroke and has had consistent high in-hospital mortality rates between 12% and 14% for more than one decade.[2-4] Pneumonia is the most common cause of community-acquired sepsis,[5,6] and timely recognition of imminent bacteremia has considerable consequences for the choice of targeted treatment. Although blood cultures (BCs) are the criterion standard for detecting bacteremia, the utility of BCs in patients with CAP is controversial.[6-11] Opinions on the importance of BCs in patients with CAP vary. Some remain unconvinced of the necessity of BCs,[12] others advocate the optional or selective use of BCs in defined subgroups of patients,[9,13] and some recommend BCs in hospitalized patients with moderate or severe CAP, particularly in patients admitted to the ICU, as stated in guidelines.[9,10,14,15]

Traditionally, fever is a classical trigger for drawing BCs.[16] Nevertheless, several reports also emphasize that bacteremia may evolve without perceivable signs of fever or hypothermia, thereby bringing into question the predictive power of temperature changes.[17] In particular, elderly patients frequently do not show classical CAP signs and symptoms including fever.[14,18] Additionally, in the adopted definition of sepsis, neither fever nor hypothermia are considered important indicators.[19] Accordingly, the search for clinical manifestations and laboratory data that may serve as predictors of bacteremia in patients with CAP continues.[20]

Therefore, the primary objectives of this study were to determine the prevalence and to discern auxiliary indicators of CAP-specific bacteremia in patients who were afebrile. The secondary objectives were the comparison of clinical outcome between different types of CAP regarding fever (febrile, afebrile, and hypothermia) and the presence or absence of bacteremia.

We performed a retrospective analysis of the occurrence of bacteremia in the absence of fever in a large cohort of 4,349 patients diagnosed with CAP in whom BCs were obtained as a mandatory part of the protocol of the multinational prospective CAPNETZ cohort study. We identified clinical and laboratory characteristics predicting the necessity for BCs in patients with afebrile CAP.

Methods

This retrospective analysis is based on data accumulated by the CAPNETZ Network[21] between October 1, 2002, and June 30, 2016. Because of the comprehensive inclusion of clinical, microbiological, and epidemiologic data, this multinational multicenter prospective cohort study addresses various aspects of the etiology, pathogenesis, diagnostics, and therapy of CAP.[22] The study[23] was performed in accordance with the amended Declaration of Helsinki. The protocol was approved by the ethical review boards of each participating clinical center (leading ethics committee "Medical Faculty of Otto-von-Guericke-Universität Magdeburg" approval No. 104/01, see Acknowledgments or www.capnetz.de for participating centers). All participants consented to their inclusion in the registry.

The inclusion criteria of the registry included patients ≥ 18 years of age and patients with CAP diagnosis confirmed by radiologic evidence of a new lung infiltrate with at least one of the following signs: cough, purulent sputum, fever, and auscultatory findings consistent with pneumonia. Fever was defined as occurrence of body temperature > 37.8°C (any site with exception of rectal measurements) or ≥ 38.3°C (rectal) at the time of CAP diagnosis according to the recommendations by Dinarello and Porat[24] and High et al.[25] Hypothermia was defined as a body temperature ≤ 35.0°C.[26] Patients who had been hospitalized for a period of 28 days preceding the start of the study and those diagnosed with severe immunosuppression (HIV infection, immunosuppressive treatment after organ or stem cell transplantation, cytostatic therapy within the last 28 days, neutropenia with < 1,000/μL neutrophil granulocytes, or systemic corticosteroid treatment with doses ≥ 20 mg of prednisone or equivalent per day for > 14 days) or active TB were excluded. Demographics, patient history, and clinical and laboratory findings were documented using standardized Internet-based case report forms, as described elsewhere.[27]

The association of the following demographic characteristics, patient history, and clinical parameters recorded at the time of admission with bacteremia in patients who were afebrile were evaluated: age; sex; antibiotic pretreatment during the 28 days preceding hospitalization; hospital admission; known neoplasms; comorbidities including chronic respiratory disease, chronic heart failure, other cardiac disease, chronic liver disease, chronic kidney disease, cerebrovascular disease, or other neurologic comorbidities; diabetes mellitus; the need for oxygen administration; mental confusion; systolic (< 90 mm Hg) and/or diastolic (≤ 60 mm Hg) hypotension; tachypnea (respiratory rate ≥ 30 breaths/min); pleural effusion; multifocal pulmonary infiltrates; positive pneumococcal urine antigen tests; and CURB-65 score ≥ 2. For laboratory parameters, sodium < 130 mmol/L, BUN ≥ 30 mg/dL, CRP > 200 mg/L, leukocytosis, and leukopenia were assessed as described previously.[28,29] Additionally, all-cause 28-day mortality was recorded for each patient.[30]

Data analysis was performed using SPSS software, version 24.0 (SPSS Inc). Differences in patients' demographic data, comorbidities, antibiotic pretreatment, and clinical signs and symptoms were compared between patients with bacteremia with and without fever and between patients with and without afebrile bacteremia. Categorical variables were expressed as frequencies and percentage of the group from which they were derived. For continuous variables, values were expressed as the median together with the first and third

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quartiles. Additionally, age, sex, severity of disease (CURB-65 score), and 28-day mortality were compared between different types of CAP (afebrile bacteremic CAP, febrile bacteremic CAP, febrile nonbacteremic CAP, afebrile nonbacteremic CAP, and hypothermic CAP) using Fisher exact test for nominal data and Kruskal-Wallis test for ordinal or numerical data. Holm-Bonferroni method was used to adjust for multiple testing.

To identify the independent predictors of afebrile bacteremia in patients, logistic regression analysis was performed. Therefore, all variables (demographics, comorbidities, antibiotic pretreatment, clinical signs and symptoms, radiologic signs or biomarkers, and laboratory parameters) were included in a single model, but then those variables that were not statistically significant ($P \geq .05$) were removed.[30]

Results

Study Cohort

Out of 11,591 patients with radiologically confirmed CAP, 4,349 patients with BCs drawn were included in this study. Although the hospital admission rate was significantly higher in patients with BCs drawn, 85.1% (3,702 of 4,349) compared with 65.6% (4,751 of 7,242) in patients without BCs ($P < .001$ by Fisher exact test), median values and interquartile ranges of the CURB-65 score did not differ between patients with and without BCs (median score, 1; interquartile range, 0-2 for both groups).

The 4,349 patients with CAP with BCs drawn were further stratified by fever (febrile: n = 2,152; afebrile: n = 2,174; hypothermia: n = 23) documented at the first patient contact. From this cohort, 353 subjects had a positive BC result. However, 61 patients with high suspicion of BC contamination because of the presence of coagulase-negative staphylococci, *Micrococcus* species, *Propionibacterium* species, *Corynebacterium* species, and *Dermabacter* species were excluded from the analysis (Fig 1). Therefore, 292 subjects (febrile: n = 190; afebrile: n = 101; hypothermia: n = 1) in whom bacteremia with CAP-specific pathogens was identified were eligible for the analysis of bacteremic cases.

Comparisons of demographics, severity of disease, and 28-day mortality between different patient subgroups (afebrile bacteremic CAP, febrile bacteremic CAP, afebrile nonbacteremic CAP, febrile nonbacteremic CAP, and hypothermic CAP) are summarized in Table 1. We observed differences in age, sex, CURB-65 score on admission, and 28-day mortality with respect to these subgroups ($P < .05$). Patients with afebrile and febrile bacteremic CAP had a higher median CURB-65 score of 2 compared with 1 for the nonbacteremic CAP subgroups. Moreover, patients with afebrile bacteremia had the numerically highest median age (70 years) and were more frequently men (64.4%) than patients with afebrile nonbacteremic CAP (55.3%). The 28-day mortality rate was more than doubled in afebrile bacteremia than febrile bacteremia (9.9% vs 3.7%, respectively) or afebrile nonbacteremic CAP (3.3%), and was comparable with the 28-day mortality rate found in hypothermic CAP (8.7%).

Bacteremia Rates, Accompanying Sputum Culture, and Spectrum of Pathogens

Positive BCs were detected in 353 of the 4,349 patients with CAP with BCs drawn (8.1%), but BC contamination was presumed in 61 of the 4,349 patients (1.4%). Therefore, bacteremia was present in 190 of 2,116 patients who were febrile (8.9%), in 101 of 2,149 patients who were afebrile (4.7%), and in 1 of 23 patients with hypothermia (4.3%). Overall bacteremia rates increased with the CURB-65 score, from 3.5% in patients with CURB-65 score of 0 to 17.1% in patients with CURB-65 score of 4. However, 100 of 238 patients with bacteremic CAP (42%) and available CURB-65 score still had a score < 2.

A positive BC had an impact on choice of targeted antibiotic therapy because initial empirical therapy was escalated in 64 of 292 patients with bacteremia (21.9%) because of antibiotic resistance (n = 16) or clinical inefficacy (n = 48) median on day 3 and was deescalated in 48 of 292 patients (16.4%) median on day 4.

The distribution of the causative bacterial pathogens in patients with bacteremia, and a further classification as common CAP-specific pathogens, likely CAP-specific pathogens, rare CAP-specific pathogens, and questionable CAP pathogens are shown in Table 2.[31-33] The predominant bloodstream pathogen in patients who were afebrile was *Streptococcus pneumoniae* (n = 54), followed by *Escherichia coli* (n = 13), *Staphylococcus aureus* (n = 10), viridans streptococci (n = 7), *Haemophilus influenzae* (n = 4), *Klebsiella* species (n = 3), and enterococci (n = 3). Additionally, *Streptococcus pyogenes*, *Morganella morganii*, *Pseudomonas aeruginosa*, *Enterobacter* species, *Serratia marcescens*, *Veillonella parvula*, and *Actinomyces odontolyticus* were detected by BCs in one patient with afebrile CAP each. There was no significant difference in the distribution of predominant CAP-specific pathogens between patients with febrile and afebrile bacteremia. In patients with hypothermia, the only pathogen identified was *S pneumoniae* (n = 1). In the subgroup of patients with bacteremia with antibiotic pretreatment (n = 34), the most common pathogens remained *S pneumoniae* (n = 9),

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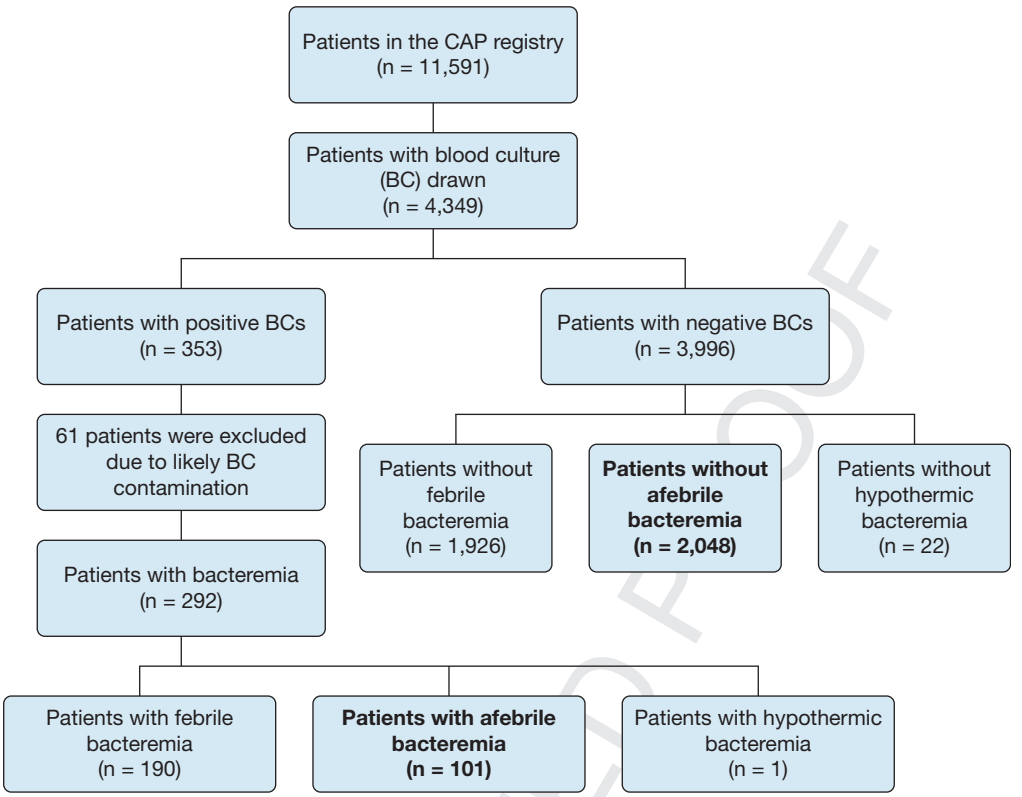

Figure 1 – *Flowchart of the study population. BC = blood culture; CAP = community-acquired pneumonia.*

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followed by *S aureus* (n = 7), viridans streptococci (n = 3), *E coli* (n = 3), and *Klebsiella* species (n = 2).

A sputum culture was available in 100 of 292 patients with bacteremia (34.2%). However, the sputum quality assessed by the Bartlett grading system was only sufficient in 49 of 292 patients with bacteremia (16.8%) and revealed a bacterial pathogen with ≥ 100,000 colony forming units/mL in 15 of 49 patients with good sputum quality: *S pneumoniae* (n = 8), *H influenzae* (n = 2), *S aureus* (n = 2), *E coli* (n = 2), and *Acinetobacter* species (n = 1). In 158 patients with *S pneumoniae* bacteremia, good quality sputum was only available in 30 patients and revealed *S pneumoniae* in 8 patients (27%), *S aureus* in 1 patient (3.3%), and *H influenzae* in 1 patient (3.3%).

Comparison of Patients With Febrile and Afebrile Bacteremia

Demographic parameters, CURB-65 score ≥ 2, comorbidities, inflammatory parameters, and most clinical features did not significantly differ (P > .05) between patients with febrile bacteremic CAP and patients with afebrile bacteremic CAP (Table 3). However, an elevated

TABLE 1] Comparison of Baseline Characteristics, CURB-65 Score, and 28-Day Mortality Rates Between Patients With CAP With Blood Culture Examination

Variable	Afebrile Bacteremic CAP (n = 101)	Febrile Bacteremic CAP (n = 190)	Afebrile Nonbacteremic CAP (n = 2,048)	Febrile Nonbacteremic CAP (n = 1,926)	Hypothermic CAP (n = 23)	*P* Value[a]
Male sex	65 (64.4)	123 (64.7)	1,133 (55.3)	1,176 (61.1)	11 (47.8)	< .001
Age, y	70 (54-78)	69 (50-79)	65 (50-76)	64 (47-74)	64 (55-72)	< .001
CURB-65 score[b]	2 (1-3)	2 (1-3)	1 (0-2)	1 (0-2)	1 (1-2)	< .001
28-d mortality	10 (9.9)	7 (3.7)	68 (3.3)	49 (2.5)	2 (8.7)	.001

Data are presented as No. (%) or median (quartile 1-quartile 3). CAP = community-acquired pneumonia.
[a]To compare the characteristics across the patient subgroups, the two-sided *P* values from a Fisher exact test in case of nominal data and a Kruskal-Wallis test in case of ordinal or numerical data are given. Given *P* values are corrected by Holm-Bonferroni method for multiple testing.
[b]Values of the CURB-65 score are missing in 23 patients with afebrile bacteremia, in 30 patients with febrile bacteremia, in 288 patients with afebrile nonbacteremic CAP, in 346 patients with febrile nonbacteremic CAP, and in 1 patient with hypothermic CAP.

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TABLE 2] List of CAP-Specific Pathogens Isolated From Blood Cultures of Patients Who Are Afebrile, Febrile, and With Hypothermia

Pathogen	All Patients[a] (n = 292)	Patients Who Are Afebrile (n = 101)	Patients Who Are Febrile (n = 190)
Common CAP-specific pathogens			
Streptococcus pneumoniae	158 (54.1)	54 (53.5)	103 (54.2)
Haemophilus influenzae	9 (3.1)	4 (4.0)	5 (2.6)
Staphylococcus aureus	23 (7.9)	10 (9.9)	13 (6.8)
Legionella pneumophila	1 (0.3)	0 (0)	1 (0.5)
Moraxella catarrhalis	1 (0.3)	0 (0)	1 (0.5)
Likely CAP-specific pathogens			
Escherichia coli	37 (12.7)	13 (12.9)	24 (12.6)
Klebsiella species	7 (2.4)	3 (3.0)	4 (2.1)
Proteus mirabilis	4 (1.4)	0 (0)	4 (2.1)
Serratia marcescens	2 (0.7)	1 (1.0)	1 (0.5)
Enterobacter species	3 (1.0)	1 (1.0)	2 (1.1)
Citrobacter species	1 (0.3)	0 (0)	1 (0.5)
Morganella morganii	1 (0.3)	1 (1.0)	0 (0)
Pseudomonas aeruginosa	4 (1.4)	1 (1.0)	3 (1.6)
Rare CAP-specific pathogens[9,31-33]			
Streptococcus agalactiae	3 (1.0)	0 (0)	3 (1.6)
Streptococcus pyogenes	4 (1.4)	1 (1.0)	3 (1.6)
Veillonella parvula	1 (0.3)	1 (1.0)	0 (0)
Prevotella species	2 (0.7)	0 (0)	2 (1.1)
Acinetobacter species	2 (0.7)	0 (0)	2 (1.1)
Actinomyces odontolyticus	1 (0.3)	1 (1.0)	0 (0)
Bacillus cereus	1 (0.3)	0 (0)	1 (0.5)
Salmonella typhimurium	1 (0.3)	0 (0)	1 (0.5)
Parvimonas micra	1 (0.3)	0 (0)	1 (0.5)
Peptostreptococcus species	1 (0.3)	0 (0)	1 (0.5)
Questionable CAP pathogens			
Enterococcus species	7 (2.4)	3 (3.0)	4 (2.1)
Viridans streptococci	16 (5.5)	7 (7.0)	9 (4.7)
Aerococcus urinae	1 (0.3)	0 (0)	1 (0.5)

Values are No. with proven bacteremia (%). See Table 1 legend for expansion of abbreviation.
[a]In patients with hypothermia, the only pathogen identified was *S pneumoniae* (n = 1).

BUN level ≥ 30 mg/dL was more frequently detected in patients with afebrile bacteremia compared with patients with febrile bacteremia (42.7% vs 25.3%, respectively; P = .005). Notably, only 3 of 292 patients with bacteremia were managed as outpatients, and all 3 of these patients were afebrile and had pneumococcal CAP. Despite initial treatment failure in 1 of the 3 patients, all of them survived at least 180 days.

Predictors of Bacteremia in Patients With Afebrile CAP

As shown in Table 4, positive pneumococcal urinary antigen test (adjusted OR [AOR], 4.6; 95% CI, 2.6-8.2), C-reactive protein (CRP) level > 200 mg/L (AOR, 3.1; 95% CI, 1.9-5.2), and BUN level ≥ 30 mg/dL (AOR, 3.1; 95% CI, 1.9-5.3) were identified as independent positive predictors, and antibiotic pretreatment (AOR, 0.3; 95% CI, 0.1-0.6) was an independent negative predictor of bacteremia in patients with afebrile CAP.

Because a bacteremia rate > 10% certainly justifies BC testing, we analyzed the impact of predictors of afebrile bacteremia, selected in the logistic regression model, on bacteremia frequencies in patients who were afebrile with and without antibiotic pretreatment

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TABLE 3] Patient Characteristics, Antimicrobial Pretreatment, Comorbidities, Clinical Features, and Laboratory Parameters in Patients With Bacteremic CAP Stratified by Presence of Fever

Variable	Patients With Afebrile Bacteremia (n = 101)	Patients With Febrile Bacteremia (n = 190)	*P* Value
Male sex	65 (64.4)	123 (64.7)	1.0
Age, y	70 (54-78)	69 (50-79)	.80
CURB-65 score ≥ 2	46/78 (59.0)	92/160 (57.5)	.90
Hospital admission	98 (97)	190 (100)	.04
Antibiotic pretreatment	11/100 (11.0)	23/189 (12.2)	.80
Comorbidities			
Neoplasia	9 (8.9)	15 (7.9)	.80
Respiratory disease	30 (29.7)	53 (27.9)	.80
Heart failure	25 (24.8)	42 (22.1)	.70
Other cardiac disease	39 (38.6)	74 (38.9)	1.0
Kidney disease	15 (14.9)	21 (11.1)	.40
Liver disease	10 (9.9)	8 (4.2)	.07
Cerebrovascular disease	9 (8.9)	30 (15.8)	.10
Other neurologic disease	7 (6.9)	13 (6.8)	1.0
Diabetes	19 (18.8)	43 (22.6)	.50
Laboratory parameters			
Leukocytosis > 12 Gpt/L	71/100 (71.0)	121/187 (64.7)	.30
Leukopenia < 4 Gpt/L	2/100 (2.0)	2/187 (1.1)	.60
C-reactive protein > 200 mg/L	59/99 (59.6)	96/188 (51.1)	.20
Sodium < 130 mmol/L	15/98 (15.3)	21/186 (11.3)	.40
BUN ≥ 30 mg/dL	38/89 (42.7)	43/170 (25.3)	.005
Clinical features			
Cough	85 (84.2)	163 (85.8)	.70
Purulent sputum	48 (47.5)	86/189 (45.5)	.80
Dyspnea	74 (73.3)	140/188 (74.5)	.90
Oxygen administration	76 (75.2)	141 (74.2)	.90
Tachypnea[a]	10/88 (11.4)	34/181 (18.8)	.20
Mental confusion	15 (14.9)	38/187 (20.3)	.30
Tachycardia[b]	32/100 (32.0)	82 (43.2)	.08
Hypotension[c]	26/99 (26.3)	53/189 (28.0)	.80
Radiologic signs or biomarkers			
Multifocal pulmonary infiltrates	14/53 (26.4)	35/94 (37.2)	.20
Pleural effusion	19/98 (19.4)	43/189 (22.8)	.30
Positive pneumococcal urine antigen	24/80 (30.0)	39/146 (26.7)	.60

Data are presented as No. (%), No./total No. (%), or median (quartile 1-quartile 3). Patients with afebrile bacteremia were compared with patients with febrile bacteremia using the χ^2 test or Fisher exact test for categorical variables and the Mann-Whitney *U* test for continuous variables. The significance level was set at $P \leq .05$. See Table 1 legend for expansion of abbreviation.

[a]Respiratory rate ≥ 30 breaths/min.

[b]Heart rate > 100 beats/min.

[c]Systolic BP < 90 mm Hg and/or diastolic BP ≤ 60 mm Hg.

(Table 5). In the absence of antibiotic pretreatment, the presence of any of the aforementioned positive risk factors was associated with a likelihood of afebrile bacteremia between 12.3% and 23.6%. In the presence of antibiotic pretreatment within the last 28 days, only a positive pneumococcal urine antigen test was associated with a likelihood of bacteremia of > 10% in patients who were afebrile.

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TABLE 4] Patient Demographics, Antimicrobial Pretreatment, Comorbidities, Clinical Features, and Laboratory Parameters in Patients With Afebrile CAP Stratified by Bacteremia

Variable	Patients With Afebrile Bacteremic CAP (n = 101)	Patients With Afebrile Nonbacteremic CAP (n = 2,048)	*P* Value[a]
Age, y	70 (54-78)	65 (50-76)	…
Male sex	65 (64.4)	1,132 (55.3)	…
CURB-65 score ≥ 2	46/78 (59.0)	605/1,760 (34.4)	…
Hospital admission	98 (97)	1,564 (76.4)	…
Antibiotic pretreatment	11/100 (11.0)	566/2,046 (27.7)	.003
Comorbidities			
Neoplasia	9 (8.9)	159/2,041 (7.8)	…
Respiratory disease	30 (29.7)	729/2,046 (35.6)	…
Heart failure	25 (24.8)	374/1,997 (18.7)	…
Other cardiac disease	39 (38.6)	652/1,997 (32.6)	…
Kidney disease	15 (14.9)	196/1,996 (9.8)	…
Liver disease	10 (9.9)	49/1,997 (2.5)	…
Cerebrovascular disease	9 (8.9)	155/1,993 (7.8)	…
Other neurologic disease	7 (6.9)	103/1,997 (5.2)	…
Diabetes	19 (18.8)	335/1,987 (16.9)	…
Clinical signs			
Cough	85 (84.2)	1,876/2,046 (91.7)	…
Purulent sputum	48 (47.5)	1,164/2,046 (56.9)	…
Dyspnea	74 (73.3)	1,437/2,042 (70.4)	…
Oxygen administration	76 (75.2)	994/2,045 (48.6)	…
Mental confusion	10/88 (11.4)	111/2,041 (5.4)	…
Tachycardia[b]	15 (14.9)	362/2,033 (17.8)	…
Tachypnea[c]	32/100 (32.0)	148/1,955 (7.0)	…
Hypotension[d]	26/99 (26.3)	390/2,037 (19.1)	…
Laboratory parameters			
C-reactive protein > 200 mg/L	71/100 (71.0)	469/2,007 (23.4)	< .001
Leukocytosis > 12 Gpt/L	59/99 (59.6)	909/2,019 (45)	…
Leukopenia < 4 Gpt/L	2/100 (2.0)	28/2,019 (1.4)	…
Sodium < 130 mmol/L	15/98 (15.3)	126/2,009 (6.3)	…
BUN ≥ 30 mg/dL	38/89 (42.7)	249/1,838 (13.5)	< .001
Radiologic signs or biomarkers			
Multifocal pulmonary infiltrates	14/53 (26.4)	414/1,560 (26.5)	…
Pleural effusion	19/98 (19.4)	313/2,022 (15.5)	…
Positive pneumococcal urinary antigen	24/80 (30.0)	87/1,653 (5.3)	< .001

Data are presented as No. (%), No./total No. (%), or median (quartile 1-quartile 3). See Table 1 legend for expansion of abbreviation.
[a]All variables were included in a single logistic regression model, but then those variables that were not statistically significant ($P \geq .05$) were removed.
[b]Heart rate > 100 beats/min.
[c]Respiratory rate ≥ 30 breaths/min.
[d]Systolic BP < 90 mm Hg and/or diastolic BP ≤ 60 mm Hg.

Discussion

Although BCs provide the most reliable evidence for the presence of bacteremia, the utility of BCs in patients with CAP is discussed controversially. Guidelines recommend the use of BCs in hospitalized patients with moderate or severe CAP, particularly in patients admitted to the ICU.[9,10,14,15] In particular, data on predictors and outcome of afebrile bacteremia are

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TABLE 5] Impact of Independent Predictors Selected in the Logistic Regression Model ($P < .05$) on Bacteremia Rates in Patients With Afebrile Community-Acquired Pneumonia and Stratified by Absence and Presence of Antibiotic Pretreatment

Variable	AOR (95% CI)	Bacteremia Rate		
		All Patients (n = 2,149)	Subgroup Without AP (n = 1,569)	Subgroup With AP (n = 577)
AP[a]				
No (n = 2,046)	Ref	5.7	5.7%	…
Yes (n = 100)	0.3 (0.1-0.6)	1.9	…	1.9
PPAT[b]				
No (n = 1,653)	Ref	3.5	4.3	1.1
Yes (n = 80)	4.6 (2.6-8.2)	21.6	23.6	13.6
CRP[c]				
No (n = 2,007)	Ref	2.5	3.1	1.1
Yes (n = 100)	3.1 (1.9-5.2)	11.2	12.3	5.8
BUN[d]				
No (n = 1,838)	Ref	3.1	3.8	1.3
Yes (n = 89)	3.1 (1.9-5.3)	13.2	15.3	3.9

AOR, adjusted OR; AP = antibiotic pretreatment; BUN = BUN ≥ 30 mg/dL, CRP = C-reactive protein > 200 mg/dL; PPAT = pneumococcal urinary antigen test.
[a]Missing information for three patients.
[b]Missing information for 416 patients.
[c]Missing information for 42 patients.
[d]Missing information for 222 patients.

rare.[34,35] To our knowledge, this is the first study to address the issue of afebrile bacteremia in CAP.

The main results of our study are subsequently discussed. More than one-third of patients with bacteremic CAP (34.6%) were afebrile. No significant differences in demographics, comorbidities, severity of disease, and inflammatory parameters were found between patients with CAP with febrile and afebrile bacteremia, but the 28-day mortality rate was more than doubled in afebrile bacteremia compared with febrile bacteremia. The distribution of main bacterial pathogens also did not differ between patients with afebrile bacteremia and patients with febrile bacteremia. Independent positive predictors of bacteremia in patients with afebrile CAP included positive pneumococcal urinary antigen test, high CRP level > 200 mg/L, and BUN level ≥ 30 mg/dL. Antibiotic pretreatment significantly reduced but did not eliminate the likelihood of bacteremia in afebrile CAP.

In line with several earlier reports,[8,12,36] the overall yield of positive BC outcomes in our observation remained < 10% (8.1%), and was even lower (6.8%) when likely BC contaminants were excluded. However, among 292 patients with bacteremia, 101 (34.6%) were afebrile at the time of BC sampling. Because of extremely low bacteremia rates in outpatients (0.6% in afebrile CAP and 0% in febrile CAP), this study supports the recommendation of the German national and international guidelines to restrict BC sampling to hospitalized patients with CAP.[9,10,15] Despite similar CURB-65 scores (median, 2) in bacteremic CAP, patients with afebrile bacteremia had the numerically highest median age (70 years) and experienced a high 28-day mortality rate (9.9% for afebrile bacteremia and 3.7% for febrile bacteremia). An earlier post hoc analysis of a prospective US cohort study documented that among patients with different foci of infection who had BCs performed in an ED, 33% of those with positive BCs were afebrile.[34] Furthermore, another retrospective cohort study of bloodstream isolates—also not limited to CAP—from 994 adults admitted to the ED of a university hospital in Taiwan similarly found a higher crude 30-day mortality rate in the afebrile group compared with the febrile group (45% vs 12%, respectively; $P < .001$). The higher mortality rate in afebrile bacteremia was attributed to older age and higher Charlson comorbidity index score.[28] Notably, in this study, 43.5% of patients with *S aureus* bacteremia would not have been identified if BC sampling was performed based on the presence of fever. This lack of identification may have dramatic consequences for the individual patient because *S aureus* bacteremia, particularly with a respiratory focus, is associated with

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the highest 90-day mortality (> 50%) compared with other foci of *S aureus* bacteremia[37,38] and requires different management compared with other etiologies of pneumonia (eg, longer treatment), according to guidelines.[38,39]

Interestingly, in our study, *E coli* was the second most common pathogen in bacteremic CAP (12.7% of patients with bacteremic CAP). More than 10 years ago, Metersky et al,[28] who investigated predictors of bacteremia in hospitalized Medicare patients with CAP (13,034 patients in the derivation cohort and 12,771 patients in the validation cohort), reported similarly high rates of *E coli* bacteremia in 12% to 14% of bacteremic CAP. Compared with bacteremia caused by the leading CAP-pathogen *S pneumoniae*, we found that *E coli* bacteremic CAP was significantly associated ($P < .05$) with higher age (median age, 77 years for *E coli* bacteremia vs 63 years for pneumococcal bacteremia) and a higher rate of chronic comorbidities, including cardiac disease, kidney disease, cerebrovascular disease, and diabetes mellitus, whereas antibiotic pretreatment was not a significant risk factor (details are given in e-Table 1). Additional infectious foci detected in patients with *E coli* bacteremia included urinary tract infection (n = 3) and cholecystitis (n = 1). However, even in patients with pneumococcal bacteremic CAP, secondary infectious foci other than pneumonia were documented, including meningitis (n = 2), pleural empyema (n = 3), septic arthritis (n = 1), urinary tract infection (n = 1), and spondylodiscitis (n = 1).

The search for clinical and laboratory findings capable of predicting bacteremia in patients with CAP was reported in three earlier large-scale studies in which analyses stratified by the presence of fever were not performed.[20,28,29] In brief, a significant association with bacteremia was found for liver comorbidity, aberrant body temperature (either fever or hypothermia), pleuritic pain, hypotension, tachycardia, tachypnea, elevated BUN level, leukocytosis or leukopenia, elevated CRP level, low thrombocyte count, low albumin level, low sodium level, and the absence of preadmission antibiotic treatment. Although none of these reports explicitly focused on patients who were afebrile, it is not surprising that we detected similar positive and negative predictors of afebrile bacteremia in our study. Although prior antibiotic exposure significantly decreased the probability of bacteremia, high inflammatory parameters (CRP level > 200 mg/L) and BUN level ≥ 30 mg/dL significantly increased the probability of bacteremia in patients with afebrile CAP. Furthermore, we identified positive pneumococcal urinary antigen test as an additional positive predictor of afebrile bacteremia. Because *S pneumoniae* remains the leading pathogen involved in CAP and is also detected by BCs in at least 10% to 15% of patients with pneumococcal pneumonia,[40] it is not surprising that positive pneumococcal urinary antigen test is also an independent predictor of pneumococcal bacteremia in patients who are afebrile.

Our study has the following limitations. First, CAPNETZ is an observational study. Despite the request by protocol to draw BCs from every patient, this was not performed in 79.4% of outpatients and 56.2% of inpatients. Despite this obvious selection bias, pneumonia severity assessed by the CURB-65 score was comparable between patients with CAP with and without BCs (median score, 1; interquartile range, 0-2 for both groups). Second, most enrolled patients were able to sign the written informed consent form by themselves; therefore, the presented cohort is biased toward younger age, lower disease severity, and lower mortality compared with data from the German mandatory reporting CAP quality assurance program.[2] Finally, a small proportion of patients included in CAPNETZ (1.2% of patients with BCs and 0.3% of patients without BCs) received concomitant treatment with low-dose corticosteroids (median, 10 mg/d prednisone), which might have impacted the presence of fever at first patient contact. However, the rate of patients with concomitant corticosteroid treatment did not significantly differ between patients who were afebrile and febrile and severe immunosuppression was an exclusion criterion.

In conclusion, a relevant proportion of patients with bacteremic CAP caused by a CAP-specific isolate were afebrile and had a doubled mortality rate compared with patients with febrile bacteremia. Although most patients with afebrile bacteremia had a CURB-65 score ≥ 2, 41% still had a score < 2. Therefore, the presence of fever or CURB-65 score ≥ 2 should not be the only triggers for BC sampling in hospitalized patients. Patients who are afebrile with positive pneumococcal urinary antigen regardless of antibiotic pretreatment and patients who are afebrile with high CRP level and elevated BUN level in the absence of antibiotic pretreatment exhibited bacteremia rates > 10% and should therefore undergo BC testing.

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