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ORIGINAL RESEARCH

Combined Bacterial Meningitis and Infective Endocarditis: When Should We Search for the Other When Either One is Diagnosed?

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ABSTRACT

Introduction: We aimed to describe patients with coexisting infective endocarditis (IE) and bacterial meningitis (BM).

Methods: We merged two large prospective cohorts, an IE cohort and a BM cohort, with only cases of definite IE and community-acquired meningitis. We compared patients who had IE and BM concurrently to patients with IE only and BM only.

Results: Among the 1030 included patients, we identified 42 patients with IE–BM (4.1%). Baseline characteristics of patients with IE–BM were mostly similar to those of patients with IE, but meningitis was the predominant presentation at admission (39/42, 92.3%). Causative pathogens were predominantly *Streptococcus pneumoniae* (18/42, 42.9%) and *Staphylococcus aureus* (14/42, 33.3%). All pneumococcal IE were associated with BM (18/18). BM due to oral and group D streptococci, *Streptococcus agalactiae*, and *S. aureus* were frequently associated with IE

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The members of the AEPEI and the COMBAT study groups are listed in the Acknowledgements section.

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(14/30, 46.7%). Three-month mortality was 28.6% in patients with IE–BM, 20.5% in patients with IE, and 16.6% in patients with BM.
Conclusions: Patients with pneumococcal IE or altered mental status during IE must be investigated for BM. Patients with *S. aureus*, oral and group D streptococcal or enterococcal BM, or unfavorable outcome in pneumococcal meningitis would benefit from an echocardiography. Patients with the dual infection have the worst prognosis. Their identification is mandatory to initiate appropriate treatment.

Keywords: Bacterial meningitis; Infective endocarditis; Echocardiography; *Staphylococcus*; *Streptococcus*; Austrian syndrome

Key Summary Points
The association of infective endocarditis (IE) and bacterial meningitis is rare but severe.
This association usually presents itself as meningitis.
Patients with pneumococcal IE or altered mental status must be investigated for meningitis.
Patients with *S. aureus*, oral and group D streptococcal or enterococcal meningitis must be investigated for endocarditis.
Unfavorable outcome in pneumococcal meningitis must be investigated for endocarditis.

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INTRODUCTION

Infective endocarditis (IE) and bacterial meningitis (BM) share low incidence, therapeutic challenges resulting from poor antibiotic diffusion to infection sites, and a mortality rate approximating 20%. Furthermore, the clinical presentation of each entity may mimic that of the other. The situation is even more complex when these two diseases develop in a single patient, given the necessity of urgent and specific therapeutic management of each condition.

This combination of IE and BM in a single patient has been described mainly through case reports. A recent Dutch nationwide cohort study on meningitis showed that 24 out of 1025 patients (2%) with BM also had IE [1]. Although the study provided original information on this rare combination, only cases initially identified with meningitis were described, without any control group reported.

To describe the natural history and clinical characteristics of this rare combination, we analyzed the cases of endocarditis–meningitis combination in a cohort of patients with IE and a cohort of patients with BM. This enabled us to compare patients with both IE and BM with patients presenting each disease alone.

METHODS

Study Design

We merged the data from the AEPEI IE cohort and the COMBAT meningitis cohort. The AEPEI IE cohort is a prospective observational study that was conducted in 2008 in seven French regions by the Association pour l'Etude et la Prevention de l'Endocardite Infectieuse (AEPEI) that included all definite cases of IE. The methods used for this study—hereafter referred to as the AEPEI IE cohort—have been described elsewhere [2]. Briefly, all physicians in public and private practice who were likely to manage patients with IE were contacted and invited with frequent reminders to report every suspected case of IE. A case report form was filled

out by a trained clinical research assistant and validated by an expert committee. The COMBAT meningitis cohort is a prospective observational study in which all cases of definite community-acquired bacterial meningitis identified in 69 French hospitals in 2013–2014 were reported, as described elsewhere [3]. Both cohorts received a 1-year follow-up.

Case Definition and Report Form

IE cases were classified by an expert committee using the modified Duke classification and only definite IE cases were considered [4]. Bacterial meningitis was defined by positive CSF (cerebrospinal fluid) culture and/or positive soluble antigen in CSF with or without cell reaction and/or positive polymerase chain reaction (PCR) in CSF and/or purpura fulminans (with or without positive CSF culture) with a PCR in blood and/or positive blood culture and CSF cell reaction. Patients with both IE and BM were compared to patients with IE only and to patients with BM only, first for all patients and then according to the causative microorganism (Streptococcaceae, *Staphylococcus aureus*).

A specific case report form was used for each cohort. Medical history, risk factors for IE, clinical presentation, laboratory and echocardiographic findings, medical and surgical treatment, and outcome were collected. Two variables were specific to the AEPEI IE cohort, namely medical or surgical procedures or situations entailing risk of bacteremia (within 3 months before hospitalization). Otherwise, most definitions from the BM cohort were similar to those of the IE cohort. Moreover, the design of the case report form, as well as the data analysis implied some common authors from the two studies [2, 3].

Furthermore, medical charts of patients with IE–BM were reviewed for the time sequence of events, the diagnosis (IE or BM) established at hospital admission, and which of the two infections pre-existed according to the medical history of patients with IE–BM in the weeks preceding hospital admission.

Statistical Methods

Continuous variables were described with median and interquartile range [IQR], and categorical variables as number of cases and percentage. Variables were compared with non-parametric tests, the Fisher's exact test for categorical variables and the Mann–Whitney–Wilcoxon test for continuous variables. All statistical analyses were performed with SAS v9.2 (SAS Institute).

Ethical and Regulatory Issues

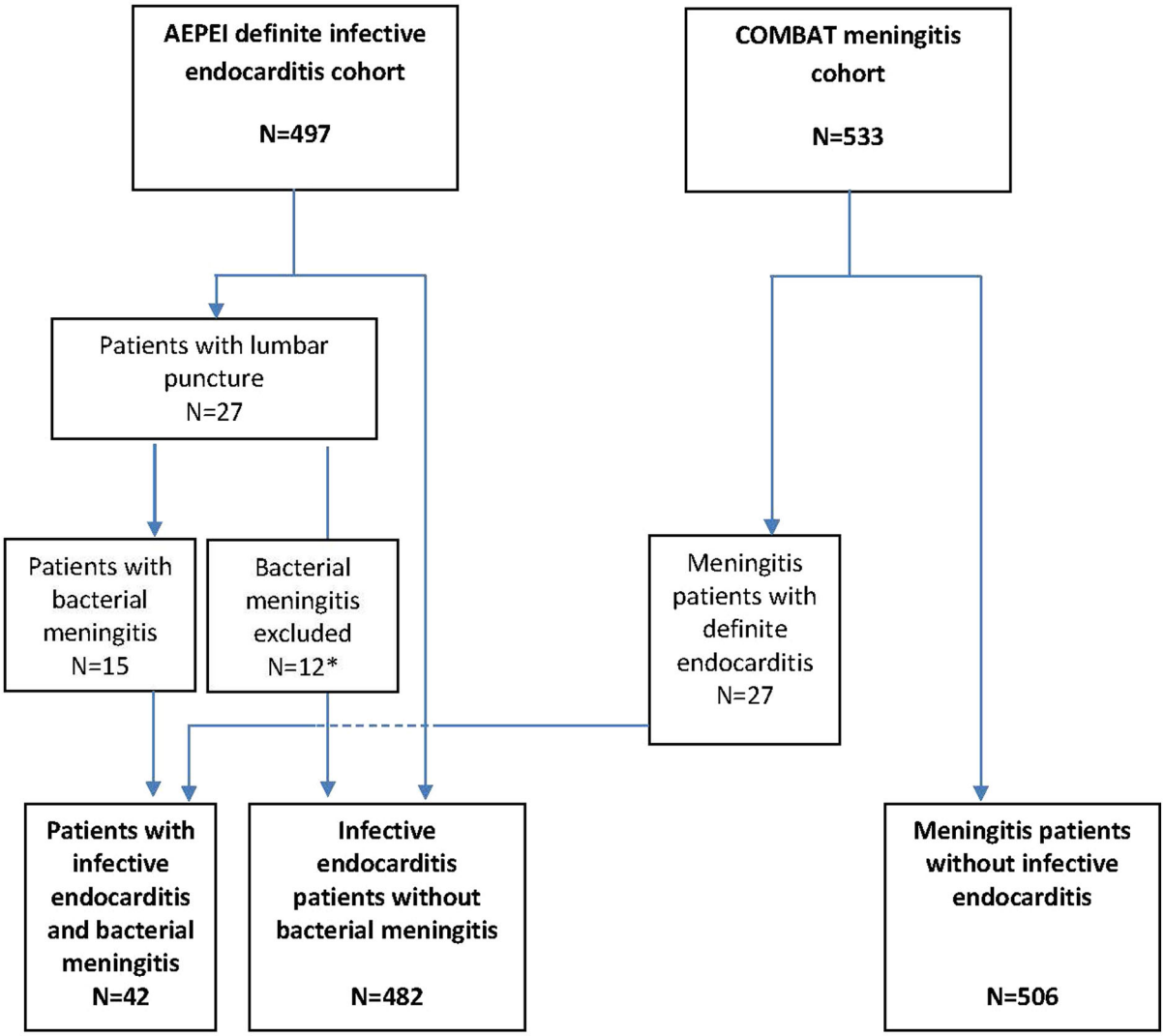
The AEPEI IE and COMBAT cohorts (ClinicalTrials.gov: NCT03272724 and NCT02916732, respectively) were approved by an institutional review board (CHU Besançon 12/2007 and CPP Ile de France CPP4 (IRB00003835) (2012-16NI), respectively) and the French data protection board (CNIL) (DR-2017-003 and EGY/FLR/AR128794, respectively). In both cohorts, patients were informed of the study orally and, in accordance with French law, did not have to provide written consent.

RESULTS

Out of the 497 patients with definite IE included in the AEPEI IE cohort, 15 patients (3%) also had meningitis. Out of the 533 patients with BM included in the COMBAT meningitis cohort, 27 (5.1%) also had definite IE. Among the 1030 patients from the merged cohorts, there were 42 patients who had both IE and meningitis (patients with IE–BM), 482 patients with IE only (patients with IE), and 506 patients with meningitis only (patients with BM) (Fig. 1).

Patients with IE–BM

Among the 42 patients with IE–BM, 31 (71.8%) were male, median age was 61 years [54.1–71.8], and 9 (21.4%) had a previously identified IE-predisposing cardiac condition. Streptococcaceae were the most frequent microorganisms



*7 patients had cerebral abscesses without meningitis, 1 patient had a cerebral abscess after a stroke, 1 patient had aseptic meningitis after multiple strokes and 1 patient had 2 normal lumbar punctures after a stroke. One patient had bacterial meningitis but IE was recoded as probable but not definite.

Fig. 1 Flowchart

(28 (66.6%) patients), including *Streptococcus pneumoniae* in 18 (42.9%) patients, and other typical IE pathogens, such as oral and group D streptococci or enterococci (Table 1). Staphylococci were represented only by *S. aureus* in 14 (33.3%) of the patients with IE–BM. Seven (16.7%) patients with IE–BM presented an Austrian syndrome (combination of pneumonia, meningitis, and endocarditis due to *S. pneumoniae*), all of them with risk factors for invasive

Table 1 Comparison of the characteristics of the three groups of patients according to the localization of the infections: infective endocarditis and meningitis, infective endocarditis only, and community acquired meningitis only

	IE and meningitis (*n* = 42)	**IE only (*n* = 482)**	***P*[a]**	**Meningitis only (*n* = 506)**	***P*[b]**	**Meningitis only excluding *N. meningitidis* (*n* = 395)**	***P*[b]**
Gender: male *n* (%)	31 (73.8)	359 (74.5)	1.000	275 (54.3)	0.015	214 (54.2)	0.015
Age (years) median [IQR]	61.0 [54.1–71.8]	64.8 [52.8–75.5] (*n* = 481)	0.341	58.2 [40.3–68.5] (*n* = 500)	0.055	61.0 [50.5–71.8] (*n* = 389)	0.609
Comorbidities							
Diabetes mellitus	9 (21.4)	110 (22.8)	1.000	71 (14.3) (*n* = 495)	0.256	67 (17.4) (*n* = 384)	0.526
Coronary diseases	4 (9.5)	58 (12.0)	0.805	21 (4.3) (*n* = 494)	0.123	21 (5.5) (*n* = 384)	0.293
Chronic cardiac failure	4 (9.5)	76 (15.8)	0.373	28 (5.6) (*n* = 497)	0.301	28 (7.3) (*n* = 386)	0.540
Chronic renal failure	5 (11.9)	57 (11.8)	1.000	20 (4.0) (*n* = 496)	0.037	19 (4.9) (*n* = 386)	0.074
Neoplasia	1 (2.4)	88 (18.3)	0.005	54 (10.8) (*n* = 498)	0.108	49 (12.7) (*n* = 387)	0.045
Liver disease	5 (11.9)	67 (13.9)	1.000	27 (5.4) (*n* = 496)	0.094	26 (6.8) (*n* = 385)	0.213
Immunodeficiency (innate or acquired, including HIV)	6 (14.3)	33 (6.8)	0.114	55 (11.0) (*n* = 499)	0.455	49 (12.6) (*n* = 388)	0.807
Alcoholism	10 (23.8)	58 (12.6) (*n* = 461)	0.056	74 (14.9) (*n* = 495)	0.181	66 (17.2) (*n* = 384)	0.291
IV drug use	2 (4.8)	28 (5.8)	1.000	NA		NA	
Hypertension	17 (40.5)	227 (47.1)	0.426	NA		NA	

Table 1 continued

	IE and meningitis (n = 42)	IE only (n = 482)	P^a	Meningitis only (n = 506)	P^b	Meningitis only excluding *N. meningitidis* (n = 395)	P^b
Cardiac condition predisposing to endocarditis							
Any	9 (21.4)						
Pre-existing valvulopathy	9 (21.4)	174 (37.0) (n = 470)	0.056	NA		NA	
Endocardial lead	1 (2.4)	65 (13.5)	0.048	NA		NA	
Symptoms and signs on presentation							
NYHA III/IV	10 (33.3) (n = 30)	97 (77.6) (n = 125)	< 0.001	NA		NA	
Time between symptom onset and hospitalization (days)	2.0 [0.0–4.0] (n = 39)	3.0 [0.0–10.0] (n = 294)	0.065	1.0 [0.0–2.0] (n = 487)	0.046	1.0 [0.0–2.0] (n = 376)	0.059
Time between symptom onset and hospitalization n (%)		(n = 488)	0.001	(n = 487)	1.000	(n = 376)	1.000
After hospitalization	1 (2.4)	31 (6.5)		13 (2.7)		12 (3.2)	
< 1 month	41 (97.6)	320 (66.7)		471 (96.7)		362 (96.3)	
1–3 months	0 (0.0)	81 (16.9)		3 (0.6)		2 (0.5)	
> 3 months	0 (0.0)	40 (8.3)		0 (0.0)		0 (0.0)	
Time between hospitalization and initiation of antibiotics(days) median [IQR]	0.0 [0.0–1.0]	2.0 [0.0–5.0] (n = 481)	< 0.001	0.0 [0.0–1.0] (n = 495)	0.011	0.0 [0.0–1.0] (n = 385)	0.053
Fever	36 (92.3) (n = 39)	406 (89.4) (n = 454)	0.785	342 (69.9) (n = 495)	0.002	280 (73.5) (n = 381)	0.010
Glasgow coma scale, median [IQR]	10.0 [9.0–13.0] (n = 29)	15.0 [15.0–15.0] (n = 416)	< 0.001	10.0 [7.0–12.0] (n = 331)	0.148	10.0 [8.0–12.0] (n = 285)	0.162

Table 1 continued

	IE and meningitis (n = 42)	IE only (n = 482)	P^a	Meningitis only (n = 506)	P^b	Meningitis only excluding *N. meningitidis* (n = 395)	P^b
Biological tests on presentation							
Blood white cells, median [IQR]	15.2 [10.6–23.7] (n = 40)	11.6 [7.8–14.9] (n = 467)	0.001	15.4 [9.9–21.0] (n = 475)	0.542	15.2 [9.9–20.4] (n = 365)	0.423
CRP, median [IQR]	258.0 [108.0–360.0] (n = 35)	103.7 [51.0–188.0] (n = 458)	< 0.001	181.5 [87.0–295.0] (n = 414)	0.061	177.0 [78.0–301.0] (n = 319)	0.056
Microorganisms		(n = 456)	< 0.001	(n = 493)	< 0.001	(n = 493)	< 0.001
Streptococcaceae	28 (66.6)	232 (50.9)					
S. pneumoniae	18 (42.9)	0 (0.0)		265 (53.8)		265 (69.4)	
S. pyogenes, Enterococcus, other streptococci (*Pneumococcus* excluded)	5 (11.9)	87 (19.1)		23 (4.7)		23 (6.0)	
Oral streptococci	4 (9.5)	83 (18.2)		7 (1.4)		7 (1.8)	
Group D streptococci	1 (2.4)	62 (13.6)		2 (0.4)		2 (0.5)	
Staphylococci	14 (33.3)	173 (37.9)					
S. aureus	14 (33.3)	125 (27.4)		4 (0.8)		4 (1.0)	
Coagulase-negative *Staphylococcus*	0 (0.0)	48 (10.5)		0 (0.0)		0 (0.0)	
N. meningitidis	0 (0.0)	0 (0.0)		111 (22.5)		0 (0.0)	
Others[c]	0 (0.0)	51 (11.2)		81 (16.4)		81 (21.2)	
≥ 2 microorganisms	0 (0.0)	9 (1.9)	1.000	0 (0.0)		0 (0.0)	
Infection origin		(n = 471)	0.002				
Community acquired	40 (95.2)	349 (74.1)		506 (100%)	NA	395 (100%)	NA
Hospital acquired	1 (2.4)	109 (23.1)		0 (0.0)		0 (0.0)	
Healthcare related but non-hospital acquired	1 (2.4)	13 (2.8)		0 (0.0)		0 (0.0)	

Table 1 continued

	IE and meningitis (n = 42)	IE only (n = 482)	P^a	Meningitis only (n = 506)	P^b	Meningitis only excluding *N. meningitidis* (n = 395)	P^b
IE characteristics							
Location of IE	(n = 41)		< 0.001				
Aortic valve	13 (31.7%)	94 (19.5%)		NA		NA	
Mitral valve	22 (53.7%)	128 (26.6%)		NA		NA	
Aortic & mitral valve	2 (4.9%)	143 (29.7%)		NA		NA	
Tricuspid valve	1 (2.4%)	34 (7.1%)		NA		NA	
Tricuspid & pulmonary	0 (0.0%)	1 (0.2%)		NA		NA	
Bilateral IE	3 (7.3%)	59 (12.2%)		NA		NA	
Endocardial lead	0 (0.0%)	14 (2.9%)		NA		NA	
Other	0 (0.0%)	2 (0.4%)		NA		NA	
Undetermined	0 (0.0%)	7 (1.5%)		NA		NA	
Vegetation	30 (71.4%)	420 (87.1%)	0.010	NA		NA	
Septic shock	20 (48.8) (n = 41)	77 (16.0)	< 0.001	NA		NA	
Left ventricular ejection fraction < 45%	3 (7.7) (n = 39)	49 (11.8) (n = 416)	0.602	NA		NA	
Cardiac abscess	7 (16.7%)	79 (16.4%)	1.000	NA		NA	
Prosthesis dehiscence	0 (0.0%) (n = 29)	20 (19.6%) (n = 102)	0.007	NA		NA	
Severe regurgitation	24 (58.5%) (n = 41)	186 (46.4%) (n = 401)	0.144	NA		NA	
Cerebrovascular complications, (a)symptomatic	21 (50.0)	123 (25.5)	0.002	128 (25.3)	0.001	111 (28.1)	0.005
Valvular surgery							

Table 1 continued

	IE and meningitis (n = 42)	IE only (n = 482)	P^a	Meningitis only (n = 506)	P^b	Meningitis only excluding *N. meningitidis* (n = 395)	P^b
Rate	18 (42.9%)	227 (47.1%)	0.632	NA		NA	
Time between surgery and hospitalization or diagnosis, median [IQR]	10.5 [2.0–19.0]	8.0 [2.0–22.0]	0.923	NA		NA	
In-hospital outcome							
Mortality at 30 days	9 (21.4)	64 (13.3)	0.161	69 (13.6)	0.169	64 (16.2)	0.386
Mortality at 3 months	12 (28.6)	99 (20.5)	0.238	84 (16.6)	0.058	79 (20.0)	0.229
Time between hospitalization and death, median [IQR]	23.0 [15.0–31.0] (n = 13)	27.0 [12.0–51.0] (n = 113)	0.463	10.0 [2.0–39.0] (n = 97)	0.134	11.0 [2.5–44.5] (n = 92)	0.200
Length of stay for survivors, median [IQR]	47.0 [30.0–58.0] (n = 30)	43.0 [27.0–66.0] (n = 481)	0.857	16.0 [11.0–29.0] (n = 359)	< 0.001	18.0 [14.0–34.0] (n = 259)	< 0.001
Length of stay, median [IQR]	44.0 [21.0–58.0] (n = 35)	46.0 [29.0–71.0] (n = 481)	0.228	15.0 [9.0–28.0] (n = 445)	< 0.001	17.0 [11.0–32.0] (n = 340)	< 0.001

We also performed the analysis for meningitis only after withdrawal of meningitis due to Neisseria meningitis

The causative microorganisms in the patients with IE–BM from the AEPEI IE cohort were Streptococcaceae (8, out of 240, 3.3%) (3 *S. pneumoniae*, 1 *Streptococcus dysgalactiae* subsp. *equisimilis*, 1 *Enterococcus faecalis*, 1 *Streptococcus oralis*, 1 *Streptococcus anginosus*, 1 *Streptococcus pyogenes*), and *S. aureus* (7, out of 180, 3.9%) (only 1 MRSA). One patient had both a *S. aureus* and *Streptococcus infantarius*

Procedure or situations entailing risk of bacteremia were specific to the AEPEI cohort. They were actively searched among the 27 patients from the COMBAT meningitis cohort but not for the patients with BM only, therefore identified in the comparison with NA. (Procedures entailing risk were dental procedures, gastrointestinal or urogenital procedures, respiratory tract procedures, skin and soft tissue procedures, cardiac catheterization. Situations entailing risk were prolonged central venous access, active intravenous drug abuse, skin and soft tissue lesion)

NA non-applicable/non-available

[a]Comparison of the patients with IE-BM to the IE population

[b]Comparison of the patients with IE–BM to the meningitis population

[c]Others included *Listeria monocytogenes* + *Haemophilus influenzae* + *E. coli* + *Mycobacterium tuberculosis* + Others + ≥ 2 microorganisms

pneumococcal disease (alcoholism (n = 5), tobacco use (n = 3), diabetes mellitus (n = 2), and AIDS (n = 1)), and a severe presentation (septic shock, heart failure, or coma), but none died. *S. pneumoniae* was the causative microorganism in half of the alcoholic patients with IE–BM.

Cerebrospinal fluid (CSF) showed pleocytosis (white cell count 450 [100–1200]) with predominance of polymorphonuclear leukocytes (PMNs) (90% [86–93]). Abnormally high protein levels in the CSF and hypoglycorrhachia were almost constantly reported. Direct identification of pathogens in CSF occurred in 22/42 patients and CSF culture was positive in 31/42. Among eight patients with negative CSF direct examination and culture, all had positive blood cultures, one had a CSF-positive antigen for pneumococci, and one a positive PCR. All patients with sterile CSF were already receiving antibiotics for more than 1 day.

At hospital admission, meningitis was diagnosed first in 39 (92.3%) out of the 42 patients with IE–BM (time between the two diagnoses of 4 [2–10] days); among these 39 patients, IE was subsequently searched for because of embolic complications (cerebral, ocular, cutaneous etc.) or cardiac failure revealing severe valve regurgitation. IE was diagnosed first in 3/42 patients (time between the two diagnoses of 1 [1–1.5] days), and meningitis was considered subsequently, given an unexplained altered mental status. A posteriori, review of the time sequence of events suggested that IE preceded meningitis in 18 patients, was simultaneous in 16 patients, posterior in 5 patients (all with *S. pneumoniae*), and undetermined in 3 patients. Endocarditis was always pre-existent or concomitant to meningitis with staphylococci.

Patients with IE–BM Compared with Patients with IE and Patients with BM

Regarding baseline characteristics, patients with IE–BM shared more similarities with patients with IE than with patients with BM, particularly for gender, age, and comorbidities.

Among all IE cases of the AEPEI cohort, 8/240 (3.3%) patients had associated Streptococcaceae BM, 7/180 (3.9%) patients had associated *S. aureus* BM, and 3/3 patients with *S. pneumoniae* IE had associated BM. Among all BM cases of the COMBAT cohort, 21/318 (6.6%) patients had associated Streptococcaceae IE (*S. pneumoniae* 15/280 (5.4%), oral streptococci 3/10, group D streptococci 2/4, *Streptococcus agalactiae* 2/5). Seven out of 11 (63.6%) patients had associated *S. aureus* IE. All in all, patients with BM from the COMBAT study with oral and group D streptococci, *S. agalactiae*, and *S. aureus* often had associated IE (14/30; 46.7%). No patients with BM with *Neisseria meningitidis* presented with IE. In absence of IE due to *N. meningitidis*, we also compared IE + BM with BM only after exclusion of the *N. meningitidis* cases.

Among patients with IE–BM, the mitral valve was the most frequently involved valve (more than 50%), followed by the aortic valve (ca. 30%), while contrary to patients with IE, other or dual localizations were exceptional. IE–BM and BM were mostly community-acquired, contrary to patients with IE, notably staphylococcus IE.

Regarding diagnosis of patients with IE–BM at hospital admission, the time interval between symptom onset and hospitalization was short, similar to meningitis or *S. aureus* IE, but differing from Streptococcaceae IE (involving a significantly longer time interval before hospitalization). Almost two-thirds of the patients with IE–BM (25/42) initially presented fever associated with altered mental status, and fever was almost constant in patients with IE–BM, patients with IE, and patients with *S. aureus* BM, but only in 73.3% of the patients with Streptococcaceae BM. Focal neurological signs appeared in the initial presentation in 8 patients out of 42, among whom four presented seizures. Glasgow coma scale was altered for patients with IE–BM and biological markers were highly elevated, similar to patients with BM, but not to patients with IE, and septic shock was significantly more frequent.

Patients with IE–BM presented more cerebrovascular events than patients with IE or BM, with no difference in cardiac surgery rate with

Table 2 Comparison of the characteristics of the three groups of patients with streptococci or staphylococci infections according to the localization of the infections: infective endocarditis and meningitis, infective endocarditis only, and community acquired meningitis only

	Streptococci					Staphylococci				
	IE + meningitis (n = 28)	IE only (n = 232)	P^a	Meningitis only (n = 297)	P^b	IE + meningitis (n = 14)	IE only (n = 125)	P^a	Meningitis only (n = 4)	P^b
Gender: male n (%)	21 (75.0)	180 (77.6)	0.812	159 (53.5)	0.030	10 (71.4)	89 (71.2)	1.000	2 (50.0)	0.569
Age (years) median [IQR]	61.0 [53.3–71.2]	65.4 [53.9–76.2]	0.214	60.6 [50.0–71.2] (n = 293)	0.596	64.1 [54.1–71.8]	62.9 [44.5–75.6]	0.992	62.7 [40.1–72.0]	0.873
Comorbidities										
Diabetes mellitus	6 (21.4)	44 (19.0)	0.800	50 (17.3) (n = 289)	0.604	3 (21.4)	30 (24.0)	1.000	1 (25.0)	1.000
Coronary diseases	4 (14.3)	21 (9.1)	0.325	19 (6.6) (n = 289)	0.133	0 (0.0)	16 (12.8)	0.370	0 (0.0)	
Chronic cardiac failure	3 (10.7)	25 (10.8)	1.000	20 (6.9) (n = 291)	0.439	1 (7.1)	24 (19.2)	0.465	1 (25.0)	0.405
Chronic renal failure	3 (10.7)	18 (7.8)	0.482	13 (4.5) (n = 291)	0.156	2 (14.3)	19 (15.2)	1.000	0 (0.0)	1.000
Neoplasia	1 (3.6)	51 (22.0)	0.022	35 (12.0) (n = 292)	0.341	0 (0.0)	15 (12.0)	0.363	0 (0.0)	
Liver disease	4 (14.3)	27 (11.6)	0.756	16 (5.5) (n = 290)	0.087	1 (7.1)	23 (18.4)	0.464	0 (0.0)	1.000
Immunodeficiency (innate or acquired, including HIV)	4 (14.3)	15 (6.5)	0.133	39 (13.3) (n = 293)	0.777	2 (14.3)	7 (5.6)	0.225	1 (25.0)	1.000
Alcoholism	9 (32.1)	29 (12.9) (n = 224)	0.020	46 (15.9) (n = 289)	0.038	1 (7.1)	20 (17.5) (n = 114)	0.464	0 (0.0)	1.000
IV drug use	1 (3.6)	3 (1.3)	0.369			1 (7.1)	21 (16.8)	0.698		
Hypertension	12 (42.9)	114 (49.1)	0.555			5 (35.7)	54 (43.2)	0.777		
Cardiac condition predisposing to endocarditis										
Any	6 (21.4)					3 (21.4)				
Pre-existing valvulopathy	6 (21.4)	89 (39.6) (n = 225)	0.079			3 (21.4)	36 (29.3) (n = 123)	0.757		
Endocardial lead	1 (3.6)	7 (3.0)	0.603			0 (0.0)	19 (15.2)	0.216		
Symptoms and signs on presentation										

Table 2 continued

	Streptococci					Staphylococci				
	IE + meningitis (*n* = 28)	**IE only (*n* = 232)**	***P*[a]**	**Meningitis only (*n* = 297)**	***P*[b]**	**IE + meningitis (*n* = 14)**	**IE only (*n* = 125)**	***P*[a]**	**Meningitis only (*n* = 4)**	***P*[b]**
NYHA III/IV	7 (31.8) (*n* = 22)	50 (78.1) (*n* = 64)	< 0.001			3 (37.5) (*n* = 8)	22 (81.5) (*n* = 27)	0.027		
Time between symptom onset and hospitalization in days	1.5 [0.0–3.0] (*n* = 26)	6.0 [1.0–19.0] (*n* = 126)	0.001	1.0 [0.0–2.0] (*n* = 284)	0.157	2.0 [0.0–4.0] (*n* = 13)	2.0 [0.0–6.0] (*n* = 97)	0.940	3.0 [2.0–4.5]	0.954
Time between symptom onset and hospitalization *n* (%)	(*n* = 28)		0.002	(*n* = 284)	1.000		(*n* = 124)	0.874		0.405
After hospitalization	0 (0.0)	8 (3.4)		8 (2.8)		1 (7.1)	11 (8.9)		1 (25.0)	
< 1 month	28 (100.0)	140 (60.3)		274 (96.5)		13 (92.9)	102 (82.3)		3 (75.0)	
1–3 months	0 (0.0)	59 (25.4)		2 (0.7)		0 (0.0)	9 (7.3)		0 (0.0)	
> 3 months	0 (0.0)	23 (9.9)		0 (0.0)		0 (0.0)	2 (1.6)		0 (0.0)	
Time between hospitalization and initiation of antibiotics (days) median [IQR]	0.0 [0.0–1.0]	2.0 [0.0–3.0]	< 0.001	0.0 [0.0–1.0] (*n* = 290)	0.044	0.5 [0.0–1.0]	1.0 [0.0–4.0]	0.039	1.5 [0.5–3.0]	0.151
Fever	25 (96.2) (*n* = 26)	195 (91.1) (*n* = 214)	0.706	209 (73.3) (*n* = 285)	0.008	11 (84.6) (*n* = 13)	118 (96.7) (*n* = 122)	0.103	4 (100.0)	1.000
Glasgow coma scale, median [IQR]	10.0 [8.0–13.0] (*n* = 19)	15.0 [15.0–15.0] (*n* = 203)	< 0.001	10.0 [7.0–12.0] (*n* = 227)	0.581	12.5 [10.0–14.0] (*n* = 10)	15.0 [14.0–15.0] (*n* = 105)	< 0.001	12.5 [12.0–13.0] (*n* = 2)	1.000
Biological tests on presentation										
Blood white cells, median [IQR]	20.6 [10.5–26.7] (*n* = 27)	10.9 [7.6–14.8] (*n* = 225)	0.005	15.4 [10.3–21.4] (*n* = 278)	0.315	15.0 [12.0–16.5] (*n* = 13)	13.0 [8.9–16.6] (*n* = 121)	0.336	17.0 [12.9–20.8] (*n* = 3)	0.420
CRP, median [IQR]	216.5 [100.0–306.0] (*n* = 22)	93.0 [54.5–142.5] (*n* = 224)	< 0.001	187.5 [91.0–318.0] (*n* = 238)	0.793	300.0 [250.0–401.0] (*n* = 13)	212.0 [121.0–293.0] (*n* = 113)	0.013	303.0 [221.0–334.0]	0.610
Microorganisms			< 0.001		< 0.001			1.000		1.000
Streptococci										
S. pneumoniae[c]	18 (64.3)	0 (0.0)		265 (89.2)		NA	NA		NA	NA
S. pyogenes + *Enterococcus* + other streptococci (*Pneumococcus* excluded)	5 (17.9)	87 (37.5)		23 (7.7)		NA	NA		NA	NA
Oral streptococci	4 (14.3)	83 (35.8)		7 (2.4)		NA	NA		NA	NA

Table 2 continued

	Streptococci					Staphylococci				
	IE + meningitis (*n* = 28)	**IE only (*n* = 232)**	***P*[a]**	**Meningitis only (*n* = 297)**	***P*[b]**	**IE + meningitis (*n* = 14)**	**IE only (*n* = 125)**	***P*[a]**	**Meningitis only (*n* = 4)**	***P*[b]**
Group D streptococci	1 (3.6)	62 (26.7)		2 (0.7)		NA	NA		NA	NA
Staphylococci										
S. aureus	NA	NA		NA	NA	14 (100.0)	125 (100.0)		4 (100.0)	
≥ 2 microorganisms	0 (0.0)	0 (0.0)	1.000	0 (0.0)	1.000	0 (0.0)	0 (0.0)	1.000	0 (0.0)	1.000
Infection origin		(*n* = 224)	0.306				(*n* = 124)	0.156		
Community	27 (96.4)	202 (90.2)				13 (92.9)	84 (67.7)			
Hospital acquired	0 (0.0)	16 (7.1)				1 (7.1)	37 (29.8)			
Non hospital acquired	1 (3.6)	6 (2.7)				0 (0.0)	3 (2.4)			
IE characteristics										
Location of IE			0.002			(*n* = 13)		0.437		
Aortic valve	9 (32.1)	47 (20.3)				4 (30.8)	23 (18.4)			
Mitral valve	15 (53.6)	64 (27.6)				7 (53.8)	37 (29.6)			
Aortic & mitral valves	1 (3.6)	86 (37.1)				1 (7.7)	28 (22.4)			
Tricuspid valve	1 (3.6)	4 (1.7)				0 (0.0)	16 (12.8)			
Tricuspid & pulmonary valve						0 (0.0)	1 (0.8)			
Bilateral valves	2 (7.1)	26 (11.2)				1 (7.7)	16 (12.8)			
Endocardial lead						0 (0.0)	3 (2.4)			
Other	0 (0.0)	2 (0.9)				0 (0.0)	1 (0.8)			
Undetermined	0 (0.0)	3 (1.3)				4 (30.8)	23 (18.4)			
Vegetation	19 (67.9)	203 (87.5)	0.010			11 (78.6)	111 (88.8)	0.380		
Septic shock	12 (44.4) (*n* = 27)	19 (8.2)	< 0.001			8 (57.1)	43 (34.4)	0.142		
FeVG < 45%	2 (7.4) (*n* = 27)	18 (8.7) (*n* = 206)	1.000			1 (8.3) (*n* = 12)	16 (15.5) (*n* = 103)	1.000		
Cardiac abscess	6 (21.4)	36 (15.5)	0.418			1 (7.1)	21 (16.8)	0.698		

Table 2 continued

	Streptococci					Staphylococci				
	IE + meningitis (n = 28)	IE only (n = 232)	P^a	Meningitis only (n = 297)	P^b	IE + meningitis (n = 14)	IE only (n = 125)	P^a	Meningitis only (n = 4)	P^b
Prosthesis dehiscence	0 (0.0) (n = 22)	8 (20.5) (n = 39)	0.042			0 (0.0) (n = 7)	3 (13.6) (n = 22)	0.558		
Severe regurgitation	19 (67.9)	106 (49.5) (n = 214)	0.074			5 (38.5) (n = 13)	36 (37.1) (n = 97)	1.000		
Cerebrovascular complications, symptomatic or not	13 (46.4)	59 (25.4)	0.025	89 (30.0)	0.088	8 (57.1)	40 (32.0)	0.077	1 (25.0)	0.577
Valvular surgery										
Rate	12 (42.9)	117 (50.4)	0.549			6 (42.9)	43 (34.4)	0.563		
Time between surgery and hospitalization or diagnosis, median [IQR]	14.5 [6.0–25.0]	7.0 [2.0–24.0]	0.296			1.5 [1.0–13.0]	8.0 [2.0–16.0]	0.221		
In-hospital outcome										
Mortality, 30 days	5 (17.9)	19 (8.2)	0.155	54 (18.2)	1.000	4 (28.6)	31 (24.8)	0.751	0 (0.0)	0.524
Mortality, 3 months	6 (21.4)	33 (14.2)	0.397	64 (21.5)	1.000	6 (42.9)	45 (36.0)	0.771	0 (0.0)	0.245
Delay between hospitalization and death, median [IQR]	26.0 [18.0–37.0]	31.0 [12.0–60.0]	0.891	9.0 [2.0–32.0]	0.035	12.0 [4.0–31.0]	23.5 [11.0–42.0]	0.203	–	–
Length of stay for survivors, median [IQR]	44.0 [30.0–57.0]	42.0 [27.0–59.5]	0.887	17.0 [14.0–30.5]	< 0.001	53.0 [26.0–65.0]	40.0 [25.0–67.0]	0.649	23.0 [7.0–63.0]	0.483
Length of stay, median [IQR]	35.0 [23.0–57.0] (n = 22)	45.0 [30.0–68.0] (n = 232)	0.212	16.0 [11.0–28.0] (n = 262)	< 0.001	53.0 [17.0–60.0] (n = 13)	40.0 [25.0–72.0]	0.838	23.0 [7.0–63.0] (n = 3)	0.736

[a]Comparison of the patients with IE-BM to the IE population

[b]Comparison of the patients with IE-BM to the meningitis population

[c]Dexamethasone use was reported only in 8/18 patients with IE–BM with *S. pneumoniae*

Table 3 Potential consequences of misdiagnosing one disease in patients with combined infective endocarditis and bacterial meningitis

If considering	*Pneumococcus*	Streptococcaceae (without *Pneumococcus*)	*S. aureus*
Meningitis only	Treatment will be too short (2 weeks vs. 4–6 weeks) Missing surgical options	Treatment will be too short (2 weeks vs. 4–6 weeks) For *E. faecalis*, an association is optimal for IE (amoxicillin + gentamicine or amoxicillin + ceftriaxone). For other Strepto, an association with Genta is often used Missing surgical options	Treatment will be too short (2–3 weeks vs. 4–6 weeks) Missing surgical options Missing association with rifampicin and gentamicin for prosthetic valve or intracardial device
IE only	Absence of dexamethasone Potentially underdosed ceftriaxone (2 g × 2 vs. 75 or 100 mg/kg/day)	Potentially underdosed ceftriaxone (2 g × 2 vs. 75 or 100 mg/kg/day)	Vancomycin may be underdosed (plasmatic target 40–60 mg/l for meningitis vs. 20–30 mg/l for IE) Cloxacillin concentrations likely to be insufficient in cerebrospinal fluid

patients with IE (42.9% vs. 47.1%, $p = 0.63$). Time interval before surgery tended to be shorter for patients with IE–BM with *S. aureus* (1.5 vs. 8.0 days) and longer for patients with Streptococcaceae IE–BM (14.5 vs. 7.0 days) (Table 2). Mortality tended to be lower among the 18 patients (42.9%) who underwent valve surgery during the initial hospital stay than among the other patients with IE–BM (2/18 (11.1%) vs. 9/24 (37.5%); $p = 0.07$). Three-month mortality was highest in patients with IE–BM (12; 28.6%), intermediate in patients with IE (99; 20.5%), and lowest in patients with BM (84; 16.6%). After withdrawal of meningococcal BM, 3-month mortality was similar in patients with BM and patients with IE. Length of hospital stay and survival were similar in patients with IE–BM and in patients with IE but significantly longer in both cases than in patients with BM (Table 1). Death tended to occur earlier (12 vs. 26 days) and more frequently (42.9% vs. 21.4%) among patients with IE–BM with *S. aureus* than in those with Streptococcaceae.

DISCUSSION

By merging two prospective cohorts, we were able to gather and describe the largest group of patients with IE–BM, to compare these patients with those with IE only and BM only, to determine their characteristics, and to propose specific care.

Association of IE and BM is a rare (3% of IE; 5% of BM) but severe condition, with a mortality rate of 28.6%, similar to the 2% rate (24/1025 BM) and 29% (7/24) mortality reported in the literature [1]. The background characteristics of the patients with IE–BM appeared closer to those of patients with IE, but most patients with IE–BM at admission seemed more comparable to patients with BM with acute presentation, and altered mental status leading to a shorter time interval between symptom onset and hospitalization and antibiotic initiation. Fever was almost systematic for patients with IE and patients with IE–BM but not for patients with BM, in accordance with the literature [5].

Precession (and potential responsibility) of one of the two diseases over the other is difficult to ascertain. Since the characteristics of the patients with IE–BM and patients with IE are similar, it seems plausible that in most cases, endocarditis preceded meningitis onset. The marked symptomatology of meningitis, as opposed to the more silent symptomatology of endocarditis, may explain why meningitis is in the foreground even though it is a complication of endocarditis. We observed that meningitis always resulted from a bacteremia and never from contiguous infectious foci, such as otitis. This is also valid for the classic Austrian syndrome [6], favored by alcoholism and immunosuppression [7]. Besides, patients with community-acquired *S. aureus* meningitis almost always present with a primary infection focus such as pneumonia or endocarditis [8, 9] and with a short time to endocarditis diagnosis (3 days in [1]). Indeed, there were only four cases of *S. aureus* BM without IE in the BM cohort, and 77.8% of BM were associated with IE. It is noticeable that patients with IE–BM were more likely to present with cerebrovascular events, with Streptococcaceae as well as *S. aureus*, in line with Servy et al. [10]. The increased risk of neurological complications usually associated with *S. aureus* [11] may result from a comparison limited to pneumococcal meningitis [1], or a limited sample size [12, 13].

Given the urgency of initiating appropriate treatment for each of these two infections (Table 3), it is necessary to identify both infections beforehand. Considering the often silent nature of cardiac damage, the main challenge is to diagnose cardiac localization during meningitis rather than the opposite. However, the negativity of 12 out of the 27 (44.4%) lumbar punctures performed in the 497 patients of the endocarditis cohort (Fig. 1), because of neurological signs, underscores the non-specificity of the neurological symptoms in patients with IE, possibly resulting from sepsis or low cardiac flow. For typically IE-responsible microorganisms (*S. aureus,* group D and oral streptococci, enterococci), IE usually appeared preceding meningitis, although the flagrant meningitis symptomatology placed it in the foreground; in such meningitis cases, we suggest performing an echocardiography, regardless of the presence or not of a previously identified IE predisposing cardiac condition. In contrast, since pneumococcus IE is rare, a lack of improvement over the course of meningitis and/or a previously known IE predisposing cardiac condition and/or another focus of infection (particularly pneumonia) should prompt an echocardiography. Indeed, early diagnosis of IE concomitant with pneumococcal meningitis is difficult and even unlikely, as IE symptoms are often non-specific, and most patients with meningitis have only one set of blood cultures performed before antibiotic initiation, because of the urgency of the situation, which limits assessment of persistent bacteremia, the most common IE diagnostic criterion. For the few patients with IE diagnosed first, the challenge is to know when to perform lumbar puncture. All our cases of pneumococcal endocarditis were associated with meningitis as were 40% of the 111 cases reported by de Egea et al. [14], suggesting the need for systematic or at least a low threshold to perform lumbar puncture in patients with pneumococcal IE. Coagulase-negative staphylococci were responsible for 10.5% of the IE cohort, but they were never isolated from a combined meningeal localization, either in the Dutch study or in ours.

Patients with IE–BM tended towards higher mortality, possibly in relation to the increased mortality associated with *S. aureus* IE [2], and a higher risk of cerebrovascular complications (ca. 50%), consistently with the Dutch study [1]. The higher mortality was not due to a different rate of cardiac surgery, as compared to patients with IE, which suggests that associated BM may not be a contraindication for cardiac surgery in patients with IE. In accordance with the literature, anticoagulants did not favor cerebrovascular complications [1, 15–17].

Our study has some limitations. Some definitions varied between the two cohorts, notably with regard to cerebrovascular complications. However, even though our new definition took into account all potentially described cerebrovascular events for homogeneity, we cannot formally rule out a reporting bias between the two cohorts. Meningitis may have been underreported in the endocarditis cohort, and

endocarditis in the meningitis cohort. Nonetheless, the population-based design of our study limits the risk of referral bias [18], its prospective design limits reporting bias, and the consistency between our cohorts and the literature suggests minimal biases. Another limitation could be a change in the epidemiology between the IE cohort which was formed in 2008, and the BM cohort, formed in 2013–2015. Notwithstanding this noticeable delay, it is unlikely that there is a significant change as IE guidelines were updated in 2015 without any changes recommended between 2008 and 2015, and the BM guidelines published in 2008 focused on treatment rather than on diagnosis. In the meantime, changes in vaccine recommendation concerned pathogens unrelated to IE or BM (such as pertussis, HPV, or MMR in 2014) and the extension of pneumococcal vaccine to adults at risk was published at the end of 2013, with a practical implementation posterior to the constitution of our BM cohort. Consequently, significant changes in the epidemiology of IE and BM between 2008 and 2015 or in physicians' practices are unlikely. Finally, the lack of precise information on the timing and doses of antibiotics precluded any analyses on the impact of appropriate medical treatment.

CONCLUSION

The combination of IE and BM is a rare event, with a dismal prognosis. Patients with pneumococcal IE or altered mental status during IE must be investigated for bacterial meningitis. Likewise, patients with *S. aureus*, oral and group D streptococcal or enterococcal MB, or unfavorable outcome in pneumococcal meningitis would benefit from blood cultures and echocardiography. Early diagnosis may allow better outcomes through timely surgery when needed, and optimal antibacterial regimen.

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Data Availability. Individual-level data will not be made publicly available with this article. Requests for sharing data for scientific research can be directed to the corresponding author. All proposals will be subject to scientific review by the AEPEI and COMBAT scientific committee.

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