DOI: 10.1161/CIRCULATIONAHA.113.001545

Endocarditis in Adults with Bacterial Meningitis

Running title: *Lucas et al.; Endocarditis in bacterial meningitis*

Marjolein J. Lucas, MD[1]; Matthijs C. Brouwer, MD, PhD[1]; Arie van der Ende, PhD[2,3]; Diederik van de Beek, MD, PhD[1]

[1]Dept of Neurology; [2]Dept of Medical Microbiology; [3]Netherlands Reference Laboratory for Bacterial Meningitis, Academic Medical Center, Center of Infection and Immunity Amsterdam (CINIMA), Amsterdam, the Netherlands

Address for Correspondence:
Diederik van de Beek, MD, PhD
Department of Neurology, Center of Infection and Immunity Amsterdam (CINIMA)
Academic Medical Center, University of Amsterdam
PO Box 22660
1100DD Amsterdam
The Netherlands
Tel: +31205663842
Fax: +31205669374
E-mail: d.vandebeek@amc.uva.nl

Journal Subject Codes: Treatment:[27] Other treatment, Cardiovascular (CV) surgery:[38] CV surgery: valvular disease, Diagnostic testing:[31] Echocardiography, Anticoagulants:[184] Coumarins, Etiology:[8] Epidemiology

DOI: 10.1161/CIRCULATIONAHA.113.001545

Abstract:

Background—Endocarditis may precede or complicate bacterial meningitis, but the incidence and impact of endocarditis in bacterial meningitis is unknown.

Methods and Results—We assessed the incidence and clinical characteristics of patients with meningitis and endocarditis from a nationwide cohort study of adults with community-acquired bacterial meningitis in the Netherlands performed from 2006 to 2012. Endocarditis was identified in 24 of 1025 (2%) episodes of bacterial meningitis. Cultures yielded *Streptococcus pneumoniae* in 13 patients, *Staphylococcus aureus* in 8 patients, and *Streptococcus agalactiae*, *Streptococcus pyogenes* and *Streptococcus salivarius* each in 1 patient. Clues leading to the diagnosis of endocarditis were cardiac murmurs, persistent or recurrent fever, a history of heart valve disease and *S. aureus* as causative pathogen of bacterial meningitis. Treatment consisted of prolonged antibiotic therapy in all patients and surgical valve replacement in 10 patients (42%). Two patients were treated with oral anticoagulants and both developed life-threatening intracerebral hemorrhage. Systemic (70%) and neurologic complications (54%) occurred frequently, leading to a high proportion of patients with unfavorable outcome (63%). Seven of 24 patients (29%) with meningitis and endocarditis died.

Conclusions—Endocarditis is an uncommon co-existing condition in bacterial meningitis, but is associated with a high rate of unfavorable outcome.

Key words: endocarditis, complication, cerebrovascular disorders, echocardiography, meningitis

DOI: 10.1161/CIRCULATIONAHA.113.001545

Introduction

Bacterial meningitis is a life-threatening disease that is associated with considerable mortality and morbidity.[1-3] To prevent death and long-term disabling sequelae caused by bacterial meningitis conjugate vaccines were developed.[4] Vaccination resulted in a sharp decrease of meningococcal disease occurrence and a moderate decrease of pneumococcal meningitis.[4] Currently *Streptococcus pneumoniae* is responsible for 70% of the cases in Europe and the US.[5] Bacterial meningitis is often related to other foci of infection outside the central nervous system, such as pneumonia, sinusitis or otitis.[1, 2, 5, 6] An uncommon focus of bacterial meningitis is infective endocarditis.[7] Endocarditis may precede or complicate bacterial meningitis, but the impact of co-existing endocarditis for patients with meningitis is unknown. We investigated the incidence, clinical features, treatment and outcome of patients with both bacterial meningitis and endocarditis identified in a nationwide cohort study of adults with community-acquired bacterial meningitis.

Methods

In a prospective nationwide observational cohort study in the Netherlands we included episodes of community-acquired bacterial meningitis confirmed by culture of cerebrospinal fluid in adults. Methods have been described in detail previously.[6] In summary, all patients were 16 years of age or older and were listed in the database of the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) from January 2006 to March 2012. This laboratory receives cerebrospinal fluid (CSF) isolates from approximately 90% of all patients with bacterial meningitis in the Netherlands. Patients with negative cerebrospinal fluid (CSF) cultures, hospital-associated meningitis, a neurosurgical device or patients who underwent a neurosurgical operation within

DOI: 10.1161/CIRCULATIONAHA.113.001545

one month before bacterial meningitis onset were excluded. Patients using immunosuppressive drugs, with asplenia, diabetes mellitus, alcoholism, or infection with immunodeficiency virus (HIV) were considered immunocompromised. Informed consent was obtained from all participating patients or their legally authorized representatives.

Clinical data were prospectively collected by means of an on-line case record form (CRF). The presence of endocarditis was scored as a standard question in the CRF. The diagnosis of endocarditis was confirmed by reanalyzing results of cardiologic analyses and echocardiography, which were collected retrospectively. Endocarditis was defined as heart valve vegetations identified by echocardiography or autopsy, or if the patient fulfilled the Duke criteria for infective endocarditis.[8, 9] At discharge, all patients underwent a neurologic examination performed by a neurologist, and outcome was graded according to the Glasgow outcome scale. This is a well-validated measurement scale with scores varying from 1 to 5.[10] A favorable outcome was defined as a score of 5, and an unfavorable outcome as a score of 1–4.

The Mann-Whitney *U* test was used to evaluate differences between bacterial meningitis patients with and without endocarditis with respect to continuous variables, and the chi-squared test and the Fisher's exact test were used to compare categorical variables. Statistical analyses were performed using IBM SPSS Statistics, version 19 and P values <0.05 were considered significant. The study was approved by the ethics committee of the Academic Medical Center, Amsterdam, the Netherlands.

Results

From January 2006 to March 2012, 1025 episodes of community-acquired bacterial meningitis were included in the cohort and endocarditis was identified in 24 of these patients (2.3%). Nine

DOI: 10.1161/CIRCULATIONAHA.113.001545

patients were female (38%) and the median age was 63 years (Q1-Q3 50-71; **Table 1**). Causative organisms were *S. pneumoniae* in 13 patients, *Staphylococcus aureus* in 8 patients, and *Streptococcus agalactiae*, *Streptococcus pyogenes* and *Streptococcus salivarius* each in 1 patient. Patients with endocarditis were more likely to have *S. aureus* as the causative pathogen compared to patients without endocarditis (8 of 24 [33%] *vs.* 6 of 1001 [1%]; P<0.001; **Table 2**).

Endocarditis was identified on admission in 3 patients (12%; all had pneumococcal meningitis), during hospitalization (19 patients, 79%; median time between admission and detection: 8 days [minimum-maximum values 2-57 days]), or after discharge (2 patients with pneumococcal meningitis, 8%). The patients with endocarditis diagnosed after discharge both had malaise, night sweats and recurrent fever. Median time between admission and detection was shorter among patients with *S. aureus* meningitis, compared to those with *S. pneumoniae* meningitis (21 patients diagnosed after admission: 3 days [Q1-Q3 3-8] vs. 16 days [Q1-Q3 9-39], P=0.015).

A cardiology consult was requested in 22 patients. Reasons for consulting a cardiologist were cardiac murmur (10 patients), persistent or recurrent fever (6 patients), pre-existing heart valve disease (3 patients), secondary clinical deterioration (3 patients), *S. aureus* as causative pathogen (3 patients), atrial flutter (2 patients), splinter hemorrhages (1 patient), or a combination of factors (2 factors in 7 patients, 3 factors in 1 patient). In three patients there was no clear reason reported for consulting a cardiologist. Two patients were not seen by a cardiologist, one patient died a few hours after admission, the other patient had no clinical suspicion of endocarditis, and the diagnosis was just made during autopsy. Endocarditis was confirmed by echocardiography in 21 patients (transesophageal in 16 patients and transthoracic in 5 patients) and by autopsy in 1 patient. Eight patients had aortic valve endocarditis, 9 patients

DOI: 10.1161/CIRCULATIONAHA.113.001545

had mitral valve endocarditis and 1 patient had tricuspid valve endocarditis. Four patients had involvement of 2 valves (aortic- and mitral valve endocarditis in 2 patients, aortic- and tricuspid valve endocarditis in 1 patient, mitral- and tricuspid valve endocarditis in 1 patient). Two patients fulfilled the Duke criteria for endocarditis without positive echocardiogram. In one of them no echocardiography was performed because the patient died a few hours after admission, in the other patient 1 transesophageal and 2 transthoracic echocardiographies were performed without clear findings of endocarditis. Blood cultures were positive on admission in all patients with endocarditis. Typical endocarditic skin lesions were reported in 6 patients (25%), and occurred more often in patients with *S. aureus* meningitis as compared to patients with *S. pneumoniae* meningitis (4 of 8 [50%] vs. 1 of 13 [8%]; P=0.05).

Patients often had predisposing conditions for infective endocarditis and immunocompromised state was identified in 8 patients, alcohol abuse in 4, heart valve disease in 3 and 1 patient had an intracardiac device.[11] Five patients (21%) presented with the triad of meningitis, endocarditis and pneumonia caused by *S. pneumonia*, known as Austrian syndrome. The majority of patients had a subacute presentation (18 of 24 [75%], defined as signs and symptoms > 24 h). Cranial CT was performed on admission in 23 patients and showed abnormalities in 7 patients: cerebral infarction (7 patients), brain edema (2 patients), and mastoid opacification and cerebral aneurysm (each in 1 patient).

The proportion of patients with at least one individual CSF finding predictive of bacterial meningitis (a glucose level of less than 34 mg/dL [1.9 mmol/L], a ratio of CSF glucose to blood glucose of less than 0.23, a protein level of more than 220 mg/dL, or a leukocyte count of more than 2,000/mm^3)[12] was lower in patients with endocarditis as compared to those without endocarditis (14 of 24 [58%] vs. 877 of 1001 [88%]; P<0.001). Endocarditis patients with *S.*

DOI: 10.1161/CIRCULATIONAHA.113.001545

aureus meningitis were less likely to have at least one individual CSF finding predictive for bacterial meningitis as described above, compared to endocarditis patients with pneumococcal meningitis (1 of 8 [13%] vs. 12 of 13 [92%]; P=0.001). CSF Gram staining was performed in 21 patients and showed bacteria in 14 patients (67%).

All patients received microbiologically adequate initial antimicrobial therapy. The median duration of antimicrobial treatment in surviving patients with endocarditis was 49 days (minimum-maximum values 28–166 days; **Table 3**). Adjunctive dexamethasone therapy was administered before or with the first dose of antibiotics in 17 of 24 patients (71%), and all received dexamethasone 10 mg 4 times daily for 4 days. Two patients received adjunctive dexamethasone after the first dose of antibiotics and the remaining 5 patients were not treated with adjunctive corticosteroid therapy.

The majority of patients developed complications during clinical course (**Table 3**). The proportion of patients with respiratory failure (13 of 23 [57%] vs. 247 of 966 [25%], P=0.001), circulatory shock (9 of 23 [39%] vs. 100 of 956 [11%], P < 0.001) and arthritis (4 of 22 [18%] vs. 27 of 948 [3%], P=0.004) was higher among patients with endocarditis as compared to those without endocarditis. Two patients with endocarditis developed spondylodiscitis and a psoas abscess (*S. aureus* and *S. pneumoniae* each in one patient). Patients with endocarditis were more likely to developed cerebral infarctions (9 of 24 [38%] vs. 222 of 1000 [22%], P=0.08) and intra-cerebral hemorrhages (3 of 24 [13%] vs. 18 of 1000 [2%], P=0.01) as compared to patients without endocarditis.

Two patients were treated with oral anticoagulants because of a history of heart valve replacement (both aortic and mitral valve replacement with mechanic valves in both patients) and both developed intracerebral hemorrhages. Cranial imaging was performed during admission

DOI: 10.1161/CIRCULATIONAHA.113.001545

in 20 patients and was abnormal in 9 patients. New abnormalities, not present on admission, were found 5 patients and consisted of cerebral infarction in 4, intracerebral hemorrhage in 3 and a brain abscess in 1 patient.

Seven of 24 (29%) patients with endocarditis died (median time after admission 25 days, minimum-maximum values 1-72 days). Unfavorable outcome occurred in 15 of 24 patients with endocarditis (63%) as compared to 386 of 1001 meningitis patients without endocarditis (39%; P=0.019). Neurologic sequelae were present on discharge in 8 of 17 (47%) survivors, consisting of cognitive impairment in 3 (18%), hemiparesis in 3 (18%), aphasia in 2 (12%), and hearing loss in 2 patients (12%).

Cardiac surgery was performed in 11 of 24 patients (6 patients with *S. aureus* and 5 patients with *S. pneumoniae* meningitis), and consisted of a valve replacement in 10 patients (6 mechanical valves, 4 bio-tissue valves of which 3 animal tissues and 1 allograft) and removal of intracardiac device (an implantable cardioverter-defibrillator) in one patient. Echocardiographic and surgical data in 10 patients who underwent valve surgery are presented in **Table 4**. Mitral valve surgery was performed in five patients; four patients got a valve replacement (3 bio-tissue valves, 1 mechanical valve), one patient got a valve repair. Four of these five patients with mitral valve surgery had large vegetations on the mitral valve with echocardiography, one patient also had an abscess on this valve and in two patients the mitral valve was perforated. Aortic valve replacement was done in six patients (1 bio-tissue valve, 5 mechanical valves); five patients had large vegetations and in one patient the aortic valve was completely destroyed.

The median time to cardiac surgery after diagnosis was 9 days (minimum-maximum values 1-45 days). In six out of ten patients surgery was performed after completion of the course of antibiotics for the meningitis. There was no difference in outcome between patients who were

DOI: 10.1161/CIRCULATIONAHA.113.001545

completely treated or partially treated for meningitis, before cardiac surgery was performed.

Nine out of 10 patients who received valve replacement survived (90%) compared to 8 of 14 patients without valve replacement (57%; P=0.17). One patient had a recurrence of prosthetic valve endocarditis 30 days after surgery, prompting surgical replacement of the prosthetic valve. Another patient underwent replacement of the prosthetic valve 5 months after surgery because the prosthetic device dehisced.

Discussion

Endocarditis is an uncommon co-existing condition in bacterial meningitis identified in 2% of patients, but is associated with high rates of unfavorable outcome (63%). Most common causative pathogens were *S. pneumoniae* and *S. aureus*, and clues leading to the diagnosis of endocarditis were cardiac murmurs, persistent or recurrent fever, a history of heart valve disease and *S. aureus* as causative pathogen of bacterial meningitis. Therefore, cardiologic consultation should be a priority in patients with community-acquired meningitis presenting with clues for endocarditis. Since about half of patients with pneumococcal meningitis have either persistent or recurrent fever,[13] many future patients with pneumococcal meningitis will need ancillary investigations to rule out or establish endocarditis. The general recommendation for antibiotic treatment duration in patients with endocarditis and meningitis is 4-6 weeks, which is substantially longer than the standard 10-14 days for meningitis patients without endocarditis.[14] Even longer courses of antibiotics are advised if the patient undergoes cardiac surgery.

Several studies suggest that combined antibiotic and surgical therapy for infective endocarditis reduces the risk of death from any cause, especially among patients who have congestive heart failure, perivalvular invasive disease, or uncontrolled infection despite maximal

DOI: 10.1161/CIRCULATIONAHA.113.001545

antimicrobial therapy.[15] In our series, although non-significant and confounded by indication, patients who underwent valve replacement had better survival compared with those without surgery (90% vs. 57%; P=0.17). The timing and indications for surgical intervention in infective endocarditis remains controversial.[16] A randomized controlled trial of 76 patients with infective endocarditis showed that early valve surgery performed within 48 hours after diagnosis, reduces the risk on death from any cause or embolic events, by reducing the risk of systemic embolism.[16] In our 10 patients with valve replacement, surgery was performed after a median of 9 days after diagnosis (minimum-maximum values 1–45 days); only 3 patients underwent valve replacement within 48 hours.

Time between admission and detection of endocarditis was substantially shorter for patients with *S. aureus* meningitis, compared to those with *S. pneumoniae* meningitis (3 days vs. 16 days). Previous studies have shown that patients with *S. aureus* meningitis almost uniformly present with a primary infection focus, most commonly pneumonia or endocarditis[17]. This suggests that in case of *S. aureus* infection endocarditis precedes bacterial meningitis, and that in bacterial meningitis caused by *S. pneumonia*, endocarditis is a complication. In case of *S. aureus* infection, meningitis is caused by septic emboli originating from cardiac valve vegetations. Our finding that fewer patients with *S. aureus* infection had individual CSF findings predictive of bacterial meningitis, as compared with patients with pneumococcal infection, is in line with this hypothesis.

Ischemic stroke is a common complication in all patients with bacterial meningitis, occurring in 22% of bacterial meningitis patients without endocarditis in our study. In a previous study we showed that cerebral infarction was present in 25% of 696 bacterial meningitis patients.[18] Ischemic stroke is also a major complication in endocarditis patients; in a previous

cohort study of 1437 patients 15.2% developed cerebral infarctions.[19] In patients with both bacterial meningitis and endocarditis there seems to be an additional risk at developing ischemic stroke; 9 out of 24 patients (38%) with both bacterial meningitis and endocarditis developed cerebral infarctions in our study.

Pneumococcal meningitis patients more often present with typical clinical and CSF characteristics of bacterial meningitis, and the possibility of endocarditis is perhaps only considered after development of complications indicative of endocarditis. Early detection of endocarditis in pneumococcal meningitis patients may lower the rate of complications and unfavorable outcome. Five of 13 patients with pneumococcal meningitis had co-existing endocarditis and pneumonia, also known as Austrian's syndrome.[7,20] All patients with Austrian's syndrome had an unfavorable outcome, reflecting the severity of this condition. Whether the primary focus of infection is the meningitis or endocarditis remains difficult to distinguish as initial complaints of endocarditis can be nonspecific.

Patients with meningitis and endocarditis should not be treated with anticoagulant therapy. Intracranial hemorrhage is a rare but devastating complication in patients with bacterial meningitis, with high rates of mortality and unfavorable outcome (65% and 95% respectively).[21] A previous study showed a 5-fold increased risk of developing intracranial hemorrhage in patients with bacterial meningitis using anticoagulant therapy.[21] Patients with *S. aureus* meningitis and endocarditis are at even higher risk of intracerebral hemorrhage compared to other bacterial meningitis patients using anticoagulant therapy.[15, 21] In these patients discontinuation of anticoagulant therapy should be considered until the patient has recovered from the acute phase of the bacterial meningitis episode.

This study has several limitations. First, several clinical characteristics of endocarditis

patients were not scored in the case record form (*e.g.* cardiac murmur, skin lesion, dental focus), which makes it difficult to determine their relevance in the diagnosis of endocarditis in meningitis patients. Furthermore, in patients with severe bacterial meningitis who died in the first day(s) of admission, endocarditis may have been missed. This could have led to an underestimation of incidence of endocarditis. Therefore, the provided incidence figures should be regarded as the minimal value. A further limitation of our study was that only patients with positive CSF cultures were included. Negative CSF cultures are estimated to occur in 11-30% of patients with bacterial meningitis.[22, 23] However, no significant differences in clinical presentation have been reported between patients with culture-positive bacterial meningitis and culture-negative bacterial meningitis. The design of our study, a prospective cohort study, precludes firm conclusions about the mechanisms explaining the association between meningitis and endocarditis; we did not have standard baseline (on admission) echocardiographic data of all our patients.

We conclude that endocarditis should be considered in patients with *S. aureus* meningitis, a history of heart valve disease, cardiac murmurs, and patients with clinical deterioration or persistent/recurrent fever during admission. Endocarditis in meningitis patients is associated with a high rate of neurologic and systemic complications, and requires prolonged antibiotic treatment and cardiac surgery in a selection of patients. Anticoagulant therapy is contraindicated in the acute phase of meningitis, as the risk of intracranial hemorrhages is high. Despite optimal antibiotic treatment, 63% of patients die or have long term neurologic sequelae.

Acknowledgements: We are indebted to all Dutch physicians who participated in the study. Author contributions: Marjolein Lucas, Matthijs Brouwer, Arie van der Ende and Diederik van de Beek performed the data analysis and wrote the manuscript. Diederik van de Beek is the principle investigator of the study and provided funding.

Funding Sources: This research has been supported by grants from the Netherlands Organization for Health Research and Development (Veni [916.76.023] and Vidi [016.116.358] to DB; Veni [916.13.078] to MB), the Academic Medical Center (AMC Fellowship 2008 to DB), and the European Research Council (ERC Starting Grant to DB).

Conflict of Interest Disclosures: None.

References:

1. van de Beek D, de Gans J, Tunkel AR, Wijdicks EF. Community-acquired bacterial meningitis in adults. *N Engl J Med*. 2006;354:44-53.

2. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med*. 2004;351:1849-1859.

3. van de Beek D. Progress and challenges in bacterial meningitis. *Lancet*. 2012;380:1623-1624.

4. McIntyre PB, O'Brien KL, Greenwood B, van de Beek D. Effect of vaccines on bacterial meningitis worldwide. *Lancet*. 2012;380:1703-1711.

5 Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. *Clin Microbiol Rev*. 2010;23:467-492.

6. Brouwer MC, Heckenberg SG, de Gans J, Spanjaard L, Reitsma JB, van de Beek D. Nationwide implementation of adjunctive dexamethasone therapy for pneumococcal meningitis. *Neurology*. 2010;75:1533-1539.

7. Angstwurm K, Halle E, Wetzel K, Schultze J, Schielke E, Weber JR. Isolated bacterial meningitis as the key syndrome of infective endocarditis. *Infection*. 2004;32:47-50.

8. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Jr., Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30:633-638.

9. Bayer AS, Ward JI, Ginzton LE, Shapiro SM. Evaluation of new clinical criteria for the diagnosis of infective endocarditis. *Am J Med*. 1994;96:211-219.

10. Jennett B, Teasdale G, Braakman R, Minderhoud J, Knill-Jones R. Predicting outcome in individual patients after severe head injury. *Lancet*. 1976;1:1031-1034.

11. Kanakadandi V, Annapureddy N, Agarwal SK, Sabharwal MS, Ammakkanavar N, Simoes P, Sanjani HP, Nadkarni GN. The Austrian syndrome: a case report and review of the literature.

Infection. 2012. DOI number 10.1007/s15010-012-0361-3.

12. Spanos A, Harrell FE, Jr., Durack DT. Differential diagnosis of acute meningitis. An analysis of the predictive value of initial observations. *JAMA*. 1989;262:2700-2707.

13. Weisfelt M, van de Beek D, Spanjaard L, Reitsma JB, de Gans J. Clinical features, complications, and outcome in adults with pneumococcal meningitis: a prospective case series. *Lancet Neurol*. 2006;5:123-129.

14. van de Beek D, Brouwer MC, Thwaites GE, Tunkel AR. Advances in treatment of bacterial meningitis. *Lancet*. 2012;380:1693-1702.

15. Mylonakis E, Calderwood SB. Infective endocarditis in adults. *N Engl J Med*. 2001;345:1318-1330.

16. Kang DH, Kim YJ, Kim SH, Sun BJ, Kim DH, Yun SC, Song JM, Choo SJ, Chung CH, Song JK, Lee JW, Sohn DW. Early surgery versus conventional treatment for infective endocarditis. *N Engl J Med*. 2012;366:2466-2473.

17. Brouwer MC, Keizerweerd GD, de Gans J, Spanjaard L, van de Beek D. Community acquired Staphylococcus aureus meningitis in adults. *Scand J Infect Dis*. 2009;1-3.

18. Schut ES, Lucas MJ, Brouwer MC, Vergouwen MD, van der Ende A, van de Beek D. Cerebral infarction in adults with bacterial meningitis. *Neurocrit Care*. 2012;16:421-427.

19. Dickerman SA, Abrutyn E, Barsic B, Bouza E, Cecchi E, Moreno A, Doco-Lecompte T, Eisen DP, Fortes CQ, Fowler VG, Jr., Lerakis S, Miro JM, Pappas P, Peterson GE, Rubinstein E, Sexton DJ, Suter F, Tornos P, Verhagen DW, Cabell CH. The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: an analysis from the ICE Prospective Cohort Study (ICE-PCS). *Am Heart J*. 2007;154:1086-1094.

20. Aronin SI, Mukherjee SK, West JC, Cooney EL. Review of pneumococcal endocarditis in adults in the penicillin era. *Clin Infect Dis*. 1998;26:165-171.

21. Mook-Kanamori BB, Fritz D, Brouwer MC, van der Ende A, van de Beek D. Intracerebral hemorrhages in adults with community associated bacterial meningitis in adults: should we reconsider anticoagulant therapy? *PLoS One*. 2012;7:e45271.

22. Durand ML, Calderwood SB, Weber DJ, Miller SI, Southwick FS, Caviness VS, Jr., Swartz MN. Acute bacterial meningitis in adults. A review of 493 episodes. *N Engl J Med*. 1993;328:21-28.

23. Sigurdardottir B, Bjornsson OM, Jonsdottir KE, Erlendsdottir H, Gudmundsson S. Acute bacterial meningitis in adults. A 20-year overview. *Arch Intern Med*. 1997;157:425-430.

DOI: 10.1161/CIRCULATIONAHA.113.001545

Table 1. Presenting symptoms of 24 bacterial meningitis patients with endocarditis [a]

Clinical characteristics	Values	Clinical characteristics	Values
Age	63 (50-71)	Focal neurologic deficits	7/24 (29%)
Female	9/24 (38%)	Aphasia	4/24 (17%)
Predisposing conditions endocarditis		Paresis	4/24 (17%)
Immunocompromised state [b]	8/24 (33%)	Blood chemistry tests [g]	
Alcoholism	4/23 (17%)	Leukocyte count (cells/mm^3)	14 (11 – 25)
Heart valve replacement	3/24 (13%)	C-reactive protein (mg/liter)	277 (194 – 349)
Intracardiac device	1/24 (4%)	ESR (mm/h)	44 (24 – 71)
Antibiotic pretreatment	0/24	Indexes of inflammation in CSF [h]	
Symptoms and signs on admission		Leukocyte count (cells/mm^3)	1184 (183–2400)
Duration of symptoms > 24 hours	17/22 (77%)	Protein (g/l)	1.4 (0.9 – 4.5)
Headache	12/17 (71%)	CSF : blood glucose ratio	0.2 (0 – 0.5)
Nausea	9/18 (50%)	CSF culture	
Temperature ≥38°C	17/22 (71%)	*Streptococcus pneumoniae*	13/24 (54%)
Triad of fever, neck stiffness, and change in mental status	10/24 (42%)	*Staphylococcus aureus*	8/24 (33%)
Neck stiffness	20/24 (83%)	Other bacteria [i]	3/24 (13%)
Seizures	1/24 (4%)	Abnormal cranial CT/MRI	7/23 (30%)
Splinter hemorrhages [c]	6	Generalized edema	1/23 (4%)
Cardiac murmur [c]	10	Hypodensity consistent with new infarction	3/23 (13%)
Systolic blood pressure (mmHg) [d]	130 (118 – 165)	Old vascular lesion	2/23 (9%)
Heart rate (beats/min) [e]	116 (90 – 130)	Mastoid opacification	1/23 (4%)
Signs of septic shock [f]	10/23 (43%)	Cerebral aneurysm	1/23 (4%)
Score on Glasgow Coma Scale	11 (9 – 14)	Austrian syndrome	5/24 (21%)
<14 (indicating change in mental status)	17/24 (71%)	Time to endocarditis diagnosis (days) (median, minimum-maximum values) [j]	9 (2 – 57)
<8 (indicating coma)	4/24 (17%)		

[a] Data are number/number evaluated (%) and continuous values are median (Q1-Q3) unless otherwise stated.
[b] Immunocompromised state is defined as the use of immunosuppressive drugs, presence of asplenia, diabetes mellitus, alcoholism, or infection with HIV
[c] Denominator unknown, not scored in the case record form
[d] Blood pressure was determined in 23 patients
[e] Heart rate was determined in 23 patients
[f] Defined as diastolic blood pressure <60 mmHg, systolic blood pressure ≤90 mmHg and/or heart rate ≥120/min
[g] Blood leukocyte count was determined in 24 patients, C-reactive protein was determined in 23 patients, ESR was determined in 15 patients
[h] CSF leukocyte count, protein level and glucose ratio were determined in 23 patients
[i] *Streptococcus agalactiae*, *Streptococcus pyogenes* and *Streptococcus salivarius*
[j] Determined in 21 patients in who endocarditis was not identified on presentation

DOI: 10.1161/CIRCULATIONAHA.113.001545

Table 2. Clinical and outcome characteristics of bacterial meningitis patients with and without endocarditis [a]

Characteristic	Endocarditis (n=24)	No endocarditis (n=1001)	*p*-value
Age (Median, Q1-Q3)	63 (50-71)	60 (45-69)	0.30
Female	9 (38%)	502 (50%)	0.22
Predisposing conditions	9/24 (38%)	570/1001 (57%)	0.06
Immunocompromised state [b]	8/24 (33%)	250/1001 (25%)	0.35
Alcoholism	4/23 (17%)	52/954 (6%)	0.04
Otitis / sinusitis	1/24 (4%)	332/998 (33%)	0.001
Pneumonia	6/24 (25%)	150/977 (15%)	0.20
Positive blood culture	24/24 (100%)	658/879 (75%)	0.005
Positive CSF gram stain	14/21 (67%)	781/910 (86%)	0.02
CSF indexes of inflammation [c]			
Protein (g/L)	1.4 (0.9-4.5)	3.9 (2.4-6.0)	0.04
CSF culture			
Streptococcus pneumoniae	13 (54%)	725 (72%)	0.05
Staphylococcus aureus	8 (33%)	6 (1%)	<0.001
Systemic complications			
Respiratory failure	13/23 (57%)	247/966 (26%)	0.001
Circulatory shock	9/23 (39%)	100/956 (11%)	<0.001
Arthritis	4/22 (18%)	27/948 (3%)	0.004
Pneumonia	7/23 (30%)	161/923 (17%)	0.20
Neurologic complications			
Cerebral infarction	9/24 (38%)	222/1000 (22%)	0.08
Intra-cerebral hemorrhage	3/24 (13%)	18/1000 (2%)	0.01
Glasgow Outcome Scale score			0.017 [d]
1 (death)	7/24 (29%)	179/1001 (18%)	
2 (vegetative state)	1/24 (4%)	0	
3 (severely disabled)	2/24 (8%)	45/1001 (5%)	
4 (moderately disabled)	5/24 (21%)	159/1001 (16%)	
5 (mild or no disability)	9/24 (38%)	615/1001 (61%)	

[a] Data are number/number evaluated (%) and continuous values are median (Q1-Q3) unless otherwise stated.
[b] Immunocompromised state is defined as the use of immunosuppressive drugs, presence of asplenia, diabetes mellitus, alcoholism, or infection with HIV
[c] CSF protein count was determined in 23 patients with endocarditis and in 950 patients without endocarditis
[d] P-value based on all 5 categories (Mann Whitney-U test)

DOI: 10.1161/CIRCULATIONAHA.113.001545

Table 3. Complications and outcome of 24 bacterial meningitis patients with endocarditis [a]

Clinical characteristics	Values
Systemic complications	16/23 (70%)
Spondylodiscitis	2/24
Psoas abscess	2/24
Respiratory failure	13/23 (57%)
Persistent fever	8/22 (36%)
Arthritis	4/22 (18%)
Pneumonia	7/23 (30%)
Neurologic complications	13/24 (54%)
Focal neurologic deficits	3/22 (14%)
Hearing impairment	3/18 (17%)
Cerebral infarction	9/24 (38%)
Intra-cerebral hemorrhage	3/24 (13%)
Brain abscess	1/24 (4%)
Duration antibiotic treatment (days, minimum-maximum values)	49 (28 - 166)
Days between admission and discharge (days)	55 (39 – 80)
Surgery	
Valve replacement	10/24 (42%)
Mechanical valve	6 (25%)
Tissue valve	4 (17%)
Removal of ICD	1 (4%)
Days between diagnosis and surgery (days, minimum-maximum values)	9 (1 – 45)
Glasgow Outcome Scale score	
1 (death)	7/24 (29%)
2 (vegetative state)	1/24 (4%)
3 (severe disability)	2/24 (8%)
4 (moderate disability)	5/24 (21%)
5 (mild or no disability)	9/24 (38%)
Neurologic sequelae	8/17 (47%)
Cognitive impairment	3/17 (18%)
Paresis	3/17 (18%)
Aphasia	2/17 (12%)
Hearing loss	2/17 (12%)

[a] Data are number/number evaluated (%) and continuous values are median (Q1-Q3) unless otherwise stated.

DOI: 10.1161/CIRCULATIONAHA.113.001545

Table 4. Echocardiographic and surgical data in 10 patients who underwent valve surgery

	Echocardiographic information	**Surgical information**
5 patients with mitral valve involvement [a]	Large vegetations (n=4) Abscess (n=1) Perforation (n=2)	Replacement (n=4) Repair (n=1) Mechanical valve (n=1) Bio-tissue valve (n=3)
6 patients with aortic valve involvement [a]	Large vegetations (n=5) Destruction (n=1)	Replacement (n=6) Mechanical valve (n=5) Bio-tissue valve (n=1)

[a] One patient had both mitral and aortic valve involvement

Endocarditis in Adults with Bacterial Meningitis

Marjolein J. Lucas, Matthijs C. Brouwer, Arie van der Ende and Diederik van de Beek

Circulation. published online April 17, 2013;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539