Factors associated with treatment delay and outcome in community acquired bacterial meningitis

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ABSTRACT

Background: Community acquired bacterial meningitis (CABM) is a condition associated with significant morbidity and mortality. Treatment delay remains an area of concern and might be improved by awareness of meningitis among health care professionals.
Methods: Retrospective observational study of patients with CABM between 2016 and 2021 in Eastern Denmark with a population of 2,700,000. Data was extracted from electronic health records. Treatment delay and mortality was analyzed using multivariate logistic regression and expressed as odds ratio (OR) with 95% confidence intervals (CI).
Results: Of 369 patients 226 (61%) had treatment delayed more than 2 hours. Old age (OR 2.42, CI 1.22;4.77), comorbidity (OR 1.30, CI 1.00;1.70), suspicion of other infections than meningitis (OR 65.93, CI 20.68;210.20), stroke (OR 7.24, CI 3.11;16.86) and other diagnoses (OR 13.00, CI 5.07;33.31) were associated with delayed treatment. Treatment delay was associated with increased 30-day mortality (OR 3.07, 95% CI 1.09;8.67). Most of the treatment delay (82%) was due lack of suspicion of CABM.
Conclusions: Treatment delay is a common problem associated with 30-day mortality in CABM. Awareness of CABM in undiagnosed patients is vital to achieve timely initiation of appropriate treatment. Special care should be shown for patients suspected of stroke or other infections.

Background

Community acquired bacterial meningitis (CABM) is a medical condition that will lead to death within hours to days if left untreated. It can be difficult to diagnose in early stages of the disease as it often presents with unspecific and trivial symptoms mimicking a wide variety of different medical conditions. Meanwhile, classical symptoms associated with CABM, such as neck stiffness, fever, and altered mental state are not always present [1,2]. Effective treatment, such as appropriate antibiotic treatment and dexamethasone, is widely available [3,4]. However, morbidity and mortality from CABM remain substantial in all parts of the world. High age, male sex and comorbidities are well known risk factors associated with poor outcome from CABM [3,5]. In recent years, several studies have found delayed diagnosis and treatment of CABM to

be a common problem associated with poor outcome [2,4,6,7]. Even a 2-hour treatment delay has been shown to increase the risk of death, and the risk increases substantially thereafter [8].

As effective treatment is available, reasons for and consequences of treatment delays remain an area in need of further research to improve outcome for patients with CABM.

During the spring of 2017, media coverage of meningitis increased in Denmark due to a TV documentary covering the tragic deaths of 3 teenagers caused by IMD. Shortly after, 11 action plans were made in the Capital Region of Denmark to improve care for patients with CABM and IMD.

We present data from 369 patients with CABM, as we aim to examine how these patients can be diagnosed and treated appropriately as quickly as possible.

Methods

Study design

We conducted a retrospective observational study of patients with CABM between January 1st of 2016 and December 31st of 2021 in the Capital Region of Denmark and in Region Zealand, which have a total population of 2,700,000 people.

As this was a quality assessment project, approval by the Committee on Health Research Ethics was not required. The need for informed consent for this study was waived by Center for Health and the Emergency Medical Services in the Capital Region of Denmark and in Health Strategic Planning in Region Zealand, who gave permission to collect, analyze, and publish data as required by Danish legislation [9].

Patient identification and data collection

Diagnosis codes for CABM (International Classification of Disease, 10th edition, (ICD-10) codes: DG00*) or invasive meningococcal disease (IMD) (ICD-10: DA39*) given to patients during hospitalization were used to identify potential CABM patients. To include potential CABM patients who were not given a diagnosis code, the regions' microbiology databases were searched for patients with either identification of bacterial pathogens in cerebrospinal fluid (CSF) or identification of *Neisseria meningitidis* in blood. All identified potential CABM patients' electronic health records (EHR) were reviewed by a physician (NH) to determine which patients had CABM based on microbiological findings in CSF or blood, biochemical findings in CSF, clinicians' descriptions of symptoms, and patient evaluations in EHR.

All data used in this study was manually extracted by NH from each patient's EHR. Appropriate treatment was defined as either treatment targeting a known etiology in doses relevant for central nervous system infections or empirical treatment as per local guidelines for suspected CABM. The time of suspicion of CABM was based on a combination of journal entries in the patient's EHR and registrations of lumbar punctures. The time of initiation of appropriate treatment was based on nurses' electronic registration of medicine administration, except in cases where more precise time points were written in the EHR. Delayed treatment was defined as initiation of appropriate treatment after more than 2 hours from hospitalization.

Comorbidity was represented in analyses as Charlson Comorbidity Index (CCI) score without points for age, because age was used as an independent factor in our analyses [10].

Media coverage was represented in analyses as per 10 mentions of the words "meningitis" or "meningokok" (meningococci) in Danish media in the 2 months leading up to the time of hospitalization. Data on media coverage was collected from TV, radio, online, or printed media via Retriever [11].

Statistical analysis

Values are given as mean and standard deviation (SD) or median and interquartile range (IQR). *P*-values between groups were calculated using Fisher's Exact Test.

Factors associated with treatment delay or 30-day mortality were analyzed using univariate and multivariate logistic regression analysis and presented as odds ratios (OR) with 95% confidence intervals (CI). Patients were grouped as children under 18 years of age, adults between 18 and 65 years of age, and elders above 65 years of age. Adjustments included sex, age group, comorbidity, pathogen, treatment delay, media coverage of meningitis, and suspected diagnosis at admission as appropriate. Directed acyclic graphs were used to select factors for adjustment (Supplementary Figure 1) and were made with DAGitty [12].

The significance threshold was set at 0.05. All statistical analyses were performed using R software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

We included 369 patients with CABM who were hospitalized between 2016 and 2021 (Supplementary Figure 2). Median age was 62 years, and 53% were male (Table 1). Adults were more often males compared to children and elders, while elders were more likely to be female compared to the other groups. All age groups were evenly distributed over the 6-year period, except for 2018 where more patients were elder and fewer patients were adults. Overall, *Streptococcus pneumoniae* was the most common cause of CABM accounting for 37% of the cases (Supplementary Figure 3). CABM in children was more likely to be caused by *Neisseria meningitidis,* while in elders it was more often caused by other bacteria. After the initial doctor's evaluation at the hospital, 47% of patients were suspected of CABM (Supplementary Figure 4). Adults with CABM were more likely to be suspected for CABM, while elders were less likely to be suspected for CABM. Children were more likely to be suspected of other infections but less likely to be suspected of stroke compared to the other groups. Elders were more likely to have treatment initiation delayed. Overall mortality was 11%, and it was higher in elders than in children and adults (19% vs 3% and 5%).

Incidence, treatment delay, and media coverage

During the 6-year period, the incidence rate was 2.3 (CI 2.1;2.5) cases per 100,000 person years at risk with an average of 61.5 cases per year (Figure 1A).

The average time from hospitalization to initiation of appropriate treatment was 10.0 hours (SD 16.0) (Figure 1B and 2A) and median time was 3.3 hours with IQR 1.2 to 9.5 hours (Figure 2B). Of that time, an average of 0.7 hours (SD 1.2, median 0.0, IQR 0.0;1.2 hours) was spent from hospitalization to first doctor's evaluation, an average of 8.2 hours (SD 15.4, median 2.3, IQR 0.5;7.8 hours) was spent from first doctor's evaluation to suspicion of CABM raised, and an average of 1.2 hours (SD 4.4, median 1.0, IQR 0.7;1.6 hours) was spent from suspicion of CABM to initiation of treatment. Appropriate treatment was initiated within 2 hours from hospitalization for 146 of the 369 patients (39%) (Figure 1C). Of the 369 patients, 136 patients (37%) received other antibiotic treatment before initiation of appropriate treatment. In those cases, average time to initiation of the other antibiotic treatment was 4.0 hours (SD 6.4, median 1.9, IQR 0.6;4.0 hours) from hospitalization.

Average media coverage of meningitis in the 2 months leading up to each patient's hospitalization was 142 mentions (SD 84, median 109, IQR 83;189 hours) (Figure 1C).

Factors associated with treatment delay

In adjusted analysis, higher age (OR 2.42 [1.22;4,77] for elders compared to adults), CABM caused by *Staphylococcus aureus* (OR 6.57 [1.93;22,33] compared to *S. pneumoniae*), CABM caused by other bacteria (OR 2.74 [1.27;5,92] compared to *S. pneumoniae*), CABM caused by unknown bacteria (OR 4.88 [1.56;15,25] compared to *S. pneumoniae*), initial suspicion of other infection (OR 65.93 [20.68;210,20] compared to meningitis), initial suspicion of stroke (OR 7.24 [3.11;16,86] compared to meningitis), initial suspicion of other diagnoses (OR 13.00 [5.07;33,31] compared to meningitis), and comorbidity (OR 1.30 [1.00;1,70] per CCI point) were all significantly associated with initiation of treatment being delayed 2 hours or more from the time of hospitalization (Table 2).

Factors associated with 30-day mortality

In adjusted analysis, male sex (OR 2.94 [1.37;6,33] compared to female sex), higher age (OR 3.31 [1.32;8,29] for elders compared to adults), treatment delay (OR 3.07 [1.09;8,67] delayed 2 hours or more

Table 1
Characteristics of 369 patients hospitalized with community acquired bacterial meningitis between 2016 and 2021 in the Capital Region of Denmark or in Region Zealand.

	All N = 369	Children <18 N = 59	P-value[A]	Adults 18-64 N = 142	P-value[B]	Elders ≥65 N = 168	P-value[C]
Gender			0.89		0.05		0.04
Female	175 (47%)	27 (46%)		58 (41%)		90 (54%)	
Male	194 (53%)	32 (54%)		84 (59%)		78 (46%)	
Year at disease							
2016	68 (18%)	7 (12%)	0.20	25 (18%)	0.78	36 (21%)	0.18
2017	55 (15%)	8 (14%)	0.84	28 (20%)	0.05	19 (11%)	0.08
2018	70 (19%)	9 (15%)	0.47	18 (13%)	0.01	43 (26%)	<0.01
2019	62 (17%)	13 (22%)	0.26	24 (17%)	1.00	25 (15%)	0.40
2020	54 (15%)	12 (20%)	0.23	22 (15%)	0.76	20 (12%)	0.19
2021	60 (16%)	10 (17%)	0.85	25 (18%)	0.66	25 (15%)	0.57
Pathogen							
Streptococcus pneumoniae	138 (37%)	16 (27%)	0.08	61 (43%)	0.10	61 (36%)	0.75
Neisseria. meningitidis	37 (10%)	18 (31%)	<0.01	15 (11%)	0.86	4 (2%)	<0.01
Haemophilus influenzae	33 (9%)	10 (17%)	0.01	8 (6%)	0.09	15 (9%)	1.00
Staphylococcus aureus	26 (7%)	0 (0%)	0.01	12 (8%)	0.41	14 (8%)	0.42
Other	105 (28%)	11 (19%)	0.08	29 (20%)	0.01	65 (39%)	<0.01
Unknown	30 (8%)	4 (7%)	0.80	17 (12%)	0.04	9 (5%)	0.09
Suspected Diagnosis [D]							
Meningitis	173 (47%)	30 (51%)	0.57	79 (56%)	0.01	64 (38%)	<0.01
Other infection	97 (26%)	26 (44%)	<0.01	24 (17%)	<0.01	47 (28%)	0.55
Stroke	48 (13%)	0 (0%)	<0.01	20 (14%)	0.64	28 (17%)	0.06
Other	51 (14%)	3 (5%)	0.04	19 (13%)	0.88	29 (17%)	0.10
Delayed treatment			0.15		0.03		<0.01
Delayed	226 (61%)	31 (53%)		70 (49%)		125 (74%)	
Non-delayed	143 (39%)	28 (47%)		72 (51%)		43 (26%)	
30-day mortality			0.04		<0.01		<0.01
Survivor	328 (89%)	57 (97%)		135 (95%)		136 (81%)	
Non-survivor	41 (11%)	2 (3%)		7 (5%)		32 (19%)	

[A] P-value for children vs. adults and elders.
[B] P-value for adults vs. children and elders.
[C] P-value for elders vs. children and adults.
[D] Suspected diagnoses after first doctor's evaluation during the hospitalization.

Table 2
Logistic regression analysis of factors associated with delayed treatment (> 2 hours) for 369 patients with community acquired bacterial meningitis.

Factor	N (%) N = 369	Crude	P-value	Adjusted	P-value
Sex					
Female	175 (47%)	1.00 (ref)		1.00 (ref)	
Male	194 (53%)	0.61 [0.40;0.93]	0.02	0.76 [0.42;1.38]	0.36
Age group					
Adults 18 - 64	142 (38%)	1.00 (ref)		1.00 (ref)	
Children < 18	59 (16%)	1.14 [0.62;2.09]	0.68	0.68 [0.25;1.87]	0.46
Elders ≥65	168 (46%)	2.99 [1.85;4.82]	<0.01	2.42 [1.22;4.77]	0.01
Charlson comorbidity index					
Per point		1.71 [1.37;2.15]	<0.01	1.30 [1.00;1.70]	0.05
Pathogen					
Streptococcus pneumoniae	138 (37%)	1.00 (ref)		1.00 (ref)	
Neisseria meningitidis	37 (10%)	1.22 [0.59;2.52]	0.59	2.65 [0.90;7.76]	0.08
Haemophilus influenzae	33 (9%)	2.66 [1.18;6.00]	0.02	2.49 [0.82;7.51]	0.11
Staphylococcus aureus	26 (7%)	3.85 [1.46;10.18]	0.01	6.57 [1.93;22.33]	<0.01
Other	105 (28%)	3.70 [2.11;6.48]	<0.01	2.74 [1.27;5.92]	0.01
Unknown	30 (8%)	2.31 [1.01;5.30]	0.04	4.88 [1.56;15.25]	0.01
Suspected Diagnosis [A]					
Meningitis	173 (47%)	1.00 (ref)		1.00 (ref)	
Other infection	97 (26%)	54.10 [18.89;154.92]	<0.01	65.93 [20.68;210.20]	<0.01
Stroke	48 (13%)	7.83 [3.71;16.53]	<0.01	7.24 [3.11;16.86]	<0.01
Other diagnoses	51 (14%)	14.63 [6.18;34.61]	<0.01	13.00 [5.07;33.31]	<0.01
Media coverage [B]					
Per 10 mentions		0.97 [0.94;0.99]	0.01	0.97 [0.93;1.00]	0.07

[A] Suspected diagnoses after first doctor's evaluation during the hospitalization.
[B] Media coverage per 10 mentions of "Meningitis" in Danish media in the 2 months prior to time of hospitalization.
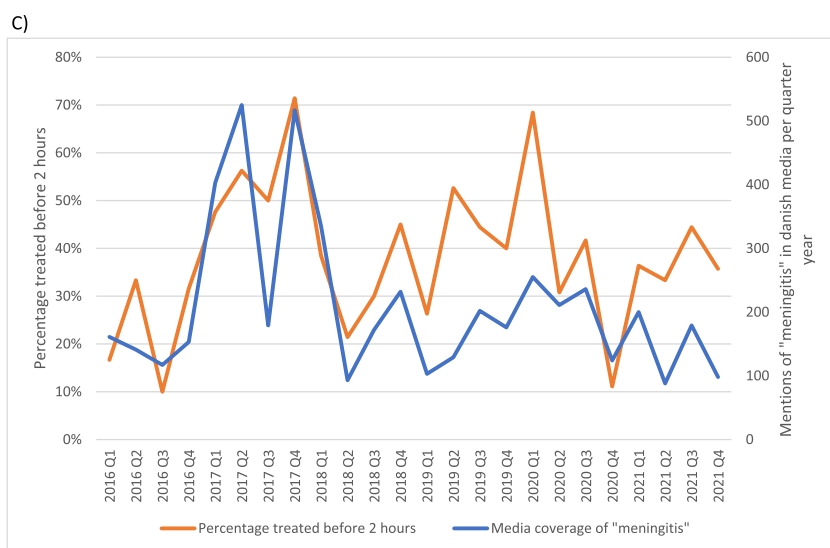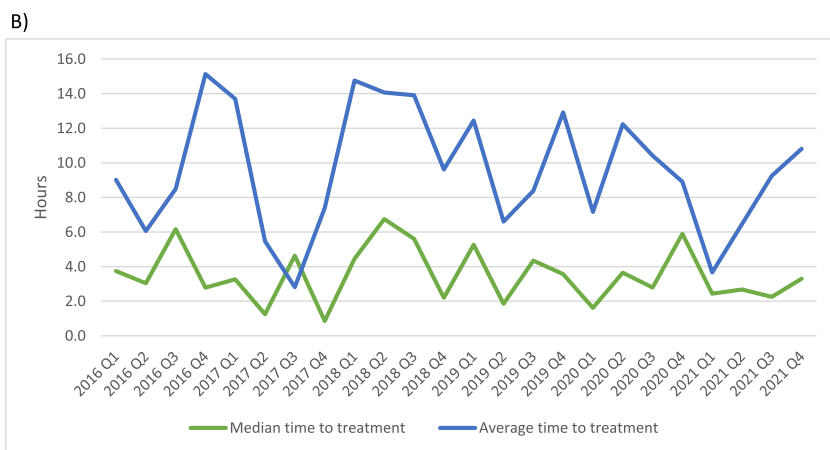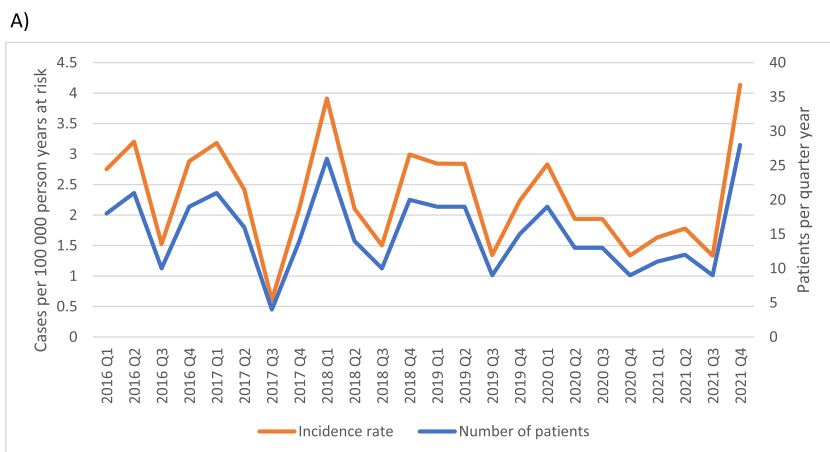
A)

Figure 1. Quarterly data for 369 patients with community acquired bacterial meningitis who were hospitalized between 2016 and 2021 in the Capital Region of Denmark or in Region Zealand. Number of patients and incidence rates (A), average and median time (hours) to treatment (B), and percentage treated within 2 hours and media coverage (C).

B)

C)

compared to not delayed), and comorbidity (OR 1.23 [1.01;1,49] per CCI point) were significantly associated with increased 30-day mortality (Table 3).

Discussion

During the 6-year period, 61% of patients with CABM had a delay of 2 hours or more from hospitalization to initiation of appropriate treatment. The suspected diagnosis at the initial doctor's evaluation was meningitis for 47% of the patients. On average, each patient had

a 10-hour treatment delay (median 3.3 hours), which was longer than data previously reported by Køster-Rasmussen et al (median 1.7 hours) and Bodilsen et al. (median 2.0 hours) but comparable to data reported by Proulx et al. (median 3.8 hours) [6,7,13]. During the time from hospitalization to initiation of treatment an average of 8.2 hours (median 2.3 hours) was the time after the initial doctor's evaluation until suspicion of meningitis was raised. We found that high age, comorbidity, CABM caused by *S. aureus*, other bacteria or unknown bacteria, and initial suspicion of diagnoses other than meningitis all were independently associated with delayed treatment.
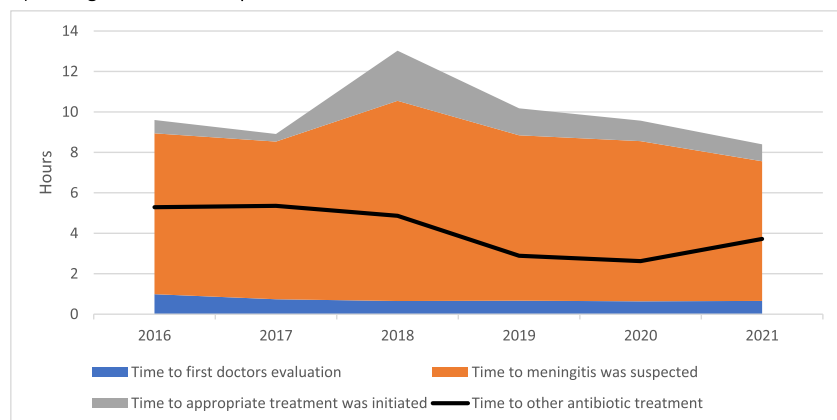
A) Average time from hospitalization

Figure 2. Average (A) and median (B) time distribution on different phases of diagnosing and treating meningitis. Of the 369 patients, 136 (37%) received other antibiotic treatment before initiation of appropriate treatment.
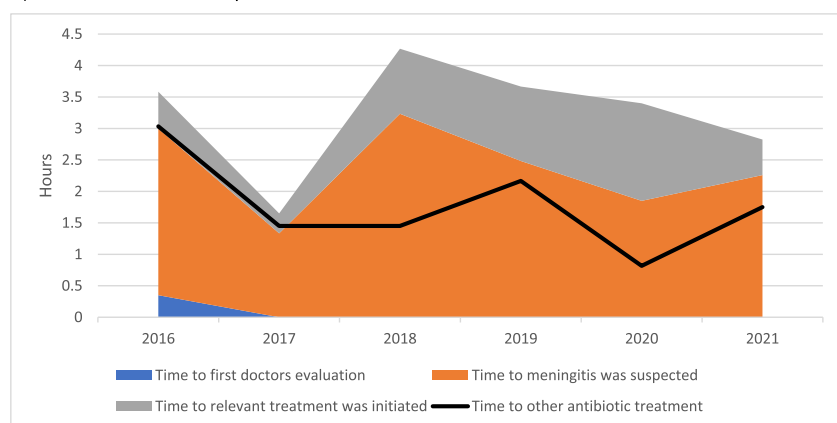
B) Median time from hospitalization

Table 3

Logistic regression analysis of factors associated with 30-day mortality for 369 patients with community acquired bacterial meningitis.

Factor	N (%)	Odds ratio with 95% confidence interval			
	N = 369	Crude	P-value	Adjusted	P-value
Sex					
Female	175 (47)	1.00 (ref)		1.00 (ref)	
Male	194 (53)	2.39 [1.18;4.84]	0.02	2.94 [1.37;6.33]	0.01
Age group					
Adults 18 - 64	142 (38)	1.00 (ref)		1.00 (ref)	
Children < 18	59 (16)	0.68 [0.14;3.36]	0.63	1.06 [0.19;5.83]	0.94
Elders ≥65	168 (46)	4.54 [1.94;10.64]	<0.01	3.31 [1.32;8.29]	0.01
Charlson comorbidity Index					
Per point		1.45 [1.24;1.69]	<0.01	1.23 [1.01;1.49]	0.03
Pathogen					
Streptococcus pneumoniae	138 (37)	1.00 (ref)		1.00 (ref)	
Neisseria meningitidis	37 (10)	0.45 [0.05;3.73]	0.46	0.66 [0.07;6.12]	0.71
Haemophilus influenzae	33 (9)	1.62 [0.41;6.49]	0.49	1.31 [0.31;5.62]	0.71
Staphylococcus aureus	26 (7)	3.87 [1.16;12.96]	0.03	2.34 [0.63;8.68]	0.21
Other	105 (28)	4.06 [1.72;9.59]	0.01	2.03 [0.79;5.23]	0.14
Unknown	30 (8)	1.81 [0.45;7.25]	0.40	1.58 [0.37;6.83]	0.54
Treatment delay					
≤2 hours		1.00 (ref)		1.00 (ref)	
>2 hours		5.23 [2.00;13.67]	<0.01	3.07 [1.09;8.67]	0.03

Our data confirms prior studies' findings that male sex, old age, co-morbidity, and delayed treatment of 2 hours or more were independently associated with higher mortality in CABM.

Male sex showed a nonsignificant tendency to have a lower OR for delayed treatment. More male patients were younger than female patients, and there were no differences between sexes in CCI (data not shown). We do not have data showing whether there were differences in other comorbidities, smoking, or alcohol consumption. Our findings could be due to male patients having more progressed disease at the time of hospitalization, which would explain more rapid diagnosis and higher mortality.

Elders were least likely to be suspected of CABM, and old age was associated with delayed treatment. This may be due to elders being more likely to have other medical conditions potentially explaining some of

the symptoms seen in CABM, e.g., stroke or sepsis with altered mental state, making the list of relevant differential diagnoses more complex for elders than for younger age groups.

Media coverage was associated with not having delayed treatment (Supplementary figure 5) when adjusted for age, sex, comorbidity, and pathogen alone. However, after further adjustment for the initial suspected diagnosis at presentation, the association was no longer statistically significant suggesting that the doctor's initial working diagnosis may also be influenced by the level of media coverage mentioning meningitis. Similarly, a study found that suspicion of CABM when patients were admitted to the hospital was associated with improved outcome [14]. Thus, we believe that doctor's awareness of meningitis as a possible diagnosis in undiagnosed patients and doctor's knowledge about the handling of patients with CABM is vital to achieve timely appropriate treatment.

A Turkish study has shown large heterogeneity in doctors' knowledge and behavior regarding diagnosing and treating CABM [15]. Other studies have shown associations between failure to follow guidelines, e.g., performing brain imaging or transferring patients between hospitals prior to antibiotic therapy, and delayed treatment [2,13].

Even though diagnosing CABM early is notoriously difficult due to nonspecific symptoms, our data shows that only 14% of patients were not suspected of either meningitis (47%), other infections (26%) or stroke (13%). Thus, focusing on evaluating patients suspected of those diagnoses for CABM could increase the chance of timely diagnosis for 86% of the patients, while repeated guideline training could improve prompt antibiotic treatment of any patient suspected for CABM which may be challenged by how seldom doctors encounter patients with CABM.

Limitations

A limitation to our study is the fact that some data, e.g., timing of antibiotic treatment, was collected from registrations entered in the EHR, which may not always be precise. However, we believe any inaccuracy in the data is minor, random, and unlikely to influence the overall conclusions drawn from our study because registration delays in most cases would be minutes, while our measure of treatment delay was hours. Our study is further limited by its retrospective nature. We attempted to include all patients with CABM by using diagnosis codes and microbiology databases but cannot exclude that a small number of cases were missed.

Conclusions

Treatment delay is a common problem associated with 30-day mortality in CABM. Awareness of CABM in undiagnosed patients is vital to achieve timely initiation of appropriate treatment.

Further research in efforts to reduce treatment delay in CABM is needed.

Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Nichlas Hovmand has nothing to disclose.

Lene Fogt Lundbo has nothing to disclose.

Gitte Kronborg has nothing to disclose.

Perle Darsø has nothing to disclose.

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Ethical approval statement

As this was a quality assessment project, approval by the Committee on Health Research Ethics was not required. The need for informed consent for this study was waived by Center for Health and the Emergency Medical Services in the Capital Region of Denmark who gave permissions to collect, analyze, and publish data as required by Danish legislation. All methods were performed in accordance with the relevant guidelines and regulations.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2023.03.013.

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