Delays in diagnosis and treatment of vaccine preventable community acquired bacterial meningitis (CABM): a retrospective analysis at three tertiary care centers

Sarah D Torres
Columbia University Medical Center
Mitashee Das
Princeton University
Carla Y Kim (ck2422@cumc.columbia.edu)
Columbia University Medical Center
Jyoti V Ankam
Columbia University Mailman School of Public Health
Nicole Luche
Cornell University Joan and Sanford I Weill Medical College
Michael Harmon
Icahn School of Medicine at Mount Sinai
Emily C Schorr
Icahn School of Medicine at Mount Sinai
Brittany Glassberg
Icahn School of Medicine at Mount Sinai
Stephen S Morse
Columbia University Mailman School of Public Health
Don Weiss
New York State Department of Health
Jacqueline S Gofshteyn
NewYork-Presbyterian Hospital/Weill Cornell Medical Center
Anusha K Yeshokumar
Icahn School of Medicine at Mount Sinai
Kiran T Thakur
Columbia University Medical Center

Research article

Keywords: bacterial meningitis, diagnostic delay, sequelae, vaccine preventable, misdiagnoses

Posted Date: January 24th, 2020

DOI: https://doi.org/10.21203/rs.2.21841/v1

Abstract

Background Outcomes in community-acquired bacterial meningitis (CABM) are significantly impacted by delays in diagnosis and treatment. This retrospective case series aims to describe the sociodemographic, epidemiological, and clinical variables including time to diagnosis and treatment of vaccine preventable CABM in three tertiary care settings in New York City (NYC).

Methods A retrospective chart review was conducted of patients at Columbia University Irving Medical Center (CUIMC), Children's Hospital of New York (CHONY), Mount Sinai Health System, and Weill Cornell Medical Center with CABM due to Haemophilus influenzae type B, Streptococcus pneumoniae, and Neisseria meningitidis between January 1, 2012 and December 31, 2017. A descriptive statistical analysis was performed.

Results Our case series consisted of 36 patients, 24 (66.7%) females, and 12 (33.33%) males with a median age of 42 years (IQR 55 years). Median time from presentation to lumbar puncture (LP) was eight hours (IQR 7). The median time from hospital presentation to diagnosis was 12 hours (IQR 9), and the median time from LP to diagnosis was three hours (IQR 5). Delay in diagnosis which is defined by more than 8 hours from hospital presentation, occurred in 13 patients (36.1%) due to initial misdiagnosis, most commonly systemic febrile and/or viral infections and otitis media.

Conclusions Despite evidence of the importance of early diagnosis and treatment for CABM, this case series shows the ongoing challenges with early clinical diagnosis. Misdiagnoses were an underlying reason for delays from presentation to LP and to antibiotic treatment in the majority of our patients. This study in NYC identifies ongoing major delays in diagnosis and antimicrobial treatment in CABM, and future studies are needed to identify mechanisms to improve time to antibiotic treatment and LP in CABM.

Background

Despite the effectiveness of vaccines in prevention of CABM, in those who acquire CABM mortality rates remain high at 10–30%, with untreated cases resulting in death within 24 to 48 hours (Glimaker et al[1], Cohn et al[2], World Health Organization 2017[3]). Prompt and effective clinical assessment are essential as delays in diagnosis and treatment were noted in one study to lead to increased mortality by 12.6% per hour and result in permanent neurological sequelae including epilepsy, hearing loss, and neurocognitive deficits in at least 20% of survivors (Glimaker et al[1], Oordt-Speets et al[4]). A prospective study of individuals diagnosed with pneumococcal meningitis found that a delay in antibiotic administration of more than three hours after presentation was independently associated with three-month mortality rates (Auburtin et al[5]). A comparable retrospective study found that the adjusted odds ratio for mortality was 8.4 times higher for those experiencing delays greater than six hours from presentation to appropriate antibiotic administration (Proulx et al[6]). This retrospective case series at three tertiary care centers in New York City (NYC) describe the sociodemographic, epidemiological, and clinical variables including time to

diagnosis and treatment of vaccine preventable CABM caused by H. influenzae, S. Pneumoniae, and N. meningitidis.

Methods

Study design

A retrospective chart review was conducted of individuals who presented to Columbia University Irving Medical Center (CUIMC), Children's Hospital of New York (CHONY), Mount Sinai Health System, and Weill Cornell Medical Center with bacterial meningitis due to Haemophilus influenzae type B, Streptococcus pneumoniae, and Neisseria meningitidis between January 1, 2012 and December 31, 2017. Electronic medical records (EMRs) of individuals discharged with ICD-9 and ICD-10 codes A39.0 (Meningococcal Meningitis), G00.0 (Hemophilus Meningitis), G00.1 (Pneumococcal Meningitis), G00.2 (Streptococcal Meningitis), 36 (Meningococcal Meningitis), 320 (Hemophilus Meningitis), 320.1 (Pneumococcal Meningitis), and 320.2 (Streptococcal Meningitis) were reviewed. All cases included in the study were cerebrospinal fluid (CSF) culture and/or polymerase chain reaction (PCR) positive for N. meningitidis, S. pneumoniae, or H. influenzae within the same admission. Unspecified bacterial meningitis (BM) discharge codes, G00.8 and G00.9, 320.82, and 320.9 were reviewed in detail but few cases were related to the three pathogens of interest. The majority of the unspecified bacterial meningitis cases stemmed from shunt infections, were CSF culture negative, or caused by low-incidence pathogenic strains not addressed in this paper. As such, these case codes were excluded from this study. Additionally, patients under two months of age and those with any surgical hardware in the brain or skull were excluded.

Sociodemographic data (age, sex, race, ethnicity, English proficiency, employment status, and household size) and epidemiologic factors (recent sick contacts, recent travel within one month of admission, chronic health conditions, daycare enrollment, alcohol, tobacco, and drug use) were gathered from EMRs. Clinical data including diagnostic evaluation, presenting symptoms, preceding illness, length of hospital and intensive care unit (ICU) stay, and need for intubation were also extracted. Time spent in the emergency department (ED) before inpatient admission, time to lumbar puncture (LP), time to etiological diagnosis defined as first positive CSF culture or CSF PCR, and time of initial central nervous system (CNS) antimicrobial coverage for BM were recorded. Glasgow Coma Scores (GCS) at presentation and Glasgow Outcome Scores (GOS) at discharge were gathered as well as the presence of hearing, behavioral and cognitive deficits, occurrence of seizures, and ability to complete tasks of daily living (ADLs) at discharge; three-to-six-month follow-up; and one-year follow-up where available. Delay from presentation to LP was defined as more than 6 hours, delayed presentation to administration of antibiotics was defined as more than 4 hours, and delay of diagnosis was defined as more than 8 hours from time of hospital admission. Descriptive statistical analyses including mean, median, standard deviation, and interquartile range were calculated for each continuous variable. Analyses were conducted using RStudio version 3.4.3 (RStudio, Boston, MA[7]) and SAS version 9.4 (SAS Institute Inc., Cary, NC[8]).

Results

Thirty-six patients presented with CABM during the study period. The median age was 42 years (IQR 55 years). There were 24 (66.7%) females and 12 (33.33%) males. Among those with racial and ethnic information available, 17 (60.7%) were Caucasian, 10 (35.7%) were Black/African-American, and one (3.6%) was of Asian descent. Six of the patients (21.4%) were Hispanic or Latino (Table 1). Eight (22.2%) patients required interpreter services. Of the thirty patients with employment status available, 8 (26.7%) were employed while 6 (20.0%) were unemployed, 4 (13.3%) were retired, 1 (3.3%) was in school and 11 (36.7%) were under the age of 5 years. Twenty-four (66.7%) of the patients in this cohort were covered by Medicaid, 4 (11.1%) by Medicare, 7 (19.4%) had private insurance and 1 (2.8%) was uninsured.

Table 1
Sociodemographic and epidemiological of patient cohort by etiology

	All		**S. Pneumoniae**		**H. Influenzae**		**N. Meningitidis**	
Sociodemographic Factors	N	%	N	%	N	%	N	%
Total	36		32		2		2	
Average Age (years)	42		42		2		1.25	
Limited English Proficiency	8	30.8	8	25.0	0	0.0	0	0.0
Epidemiological Factors								
Total Immunocompromised	16	44.4	16	50.0	0	0.0	0	0.0
Anatomical defect	2	5.6	2	6.3	0	0.0	0	0.0
Sinus	1	50.0	1	50.0	0	0.0	0	0.0
Ear	0	0.0	0	0.0	0	0.0	0	0.0
Lymphatic	1	50.0	1	50.0	0	0.0	0	0.0
Chronic infections	6	16.7	6	18.8	0	0.0	0	0.0
Recent illness	24	66.7	4	11.1	1	50.0	2	100
Alcohol use in past year	13	36.1	13	40.6	0	0.0	0	0.0
Tobacco use in past year	8	22.2	8	25.0	0	0.0	0	0.0
Drug use in past year	7	19.4	7	21.9	0	0.0	0	0.0

S. pneumoniae was identified in 32 (88.9%) cases, N. meningitidis in 2 (5.6%), and H. influenzae in 2 (5.6%). Sixteen (44.4%) individuals were immunocompromised, 6 (16.7%) reported chronic sinus, upper respiratory, or ear infections, and 24 (66.7%) reported a preceding illness other than meningitis in the 28 days leading up to presentation (Table 1). Twelve (33.3%) individuals presented to an outpatient clinic prior to admission, with 2 individuals (5.6%) admitted directly from a primary care clinic. Twenty-four (66.7%) patients initially presented to the ED of study sites with a median stay of 8 hours (IQR 6), and 11 individuals (30.6%) were transferred from an outside hospital (OSH). Ten (27.8%) of these transfer patients had been diagnosed and had begun treatment at the OSH before being transferred for further management.

The median number of days from initial neurological symptom to presentation at any clinical setting (OSH, clinic, or ED at one of our study sites) was one day (IQR 2 days). For individuals whose records included detailed time data (34, 94.4%), the median time from presentation to LP was 8 hours (IQR 7). The median time from presentation at hospital to diagnosis, defined as the first positive CSF culture or PCR result, was 12 hours (IQR 9), and the median time from LP to diagnosis was 3 hours (IQR 5). The median time from presentation to administration of CNS antimicrobial coverage was 4 hours (IQR 5). Diagnosis was delayed, defined by more than 8 hours, in 13 patients (36.1%) due to initial misdiagnosis at either an outpatient clinic, OSH, or ED. The most common misdiagnoses were systemic febrile and/or viral infections not otherwise specified (5, 13.9%) and otitis media (2, 5.6%). Other initial diagnoses included stroke (1, 2.8%), drug overdose (1, 2.8%), alcohol withdrawal (1, 2.8%), mechanical problems relating to a recent injury or fall (1, 2.8%), post-epidural headache (1, 2.8%), and neuroleptic malignant syndrome (1, 2.8%). Seventeen patients (47.2%) had a delay of more than six hours from presentation to LP. Of those, 11 (64.7%) were delayed as a result of initial misdiagnosis, two (11.8%) due to the health care proxy's hesitancy to consent to LP, and one (5.9%) was deferred out of concern for cerebral edema. Two (5.6%) patients, who were initially misdiagnosed, were non-English speaking. Five individuals (13.9%) had a delay of four hours or more from presentation to the administration of antibiotics with appropriate CNS coverage. All of these antibiotic administration delays were due to initial misdiagnosis (Table 4).

The median length of hospital stay at the three study sites was 12 days (IQR 15), and 31 (86.1%) individuals were admitted to the ICU for a median stay of 6 days (IQR 6). Nineteen (52.7%) individuals were intubated, 11 (30.6%) had seizures, 3 (8.3%) of whom were in status epilepticus, and 8 (22.2%) had cerebral edema (Table 2). Twenty-seven patients (75%) had GOS greater than or equal to 4 at discharge, while 4 patients (11.1%) expired. Upon discharge, 11 (30.6%) reported hearing loss, 3 (8.3%) seizures, 16 (44.4%) behavioral and cognitive deficits, and 11 (30.6%) were unable to complete ADLs. Of the 23 (63.9%) of patients with follow-up information available at three-to-six-month, 8 (34.8%) reported hearing loss, two (8.7%) seizures, 12 (52.2%) behavioral and cognitive deficits, and 5 (21.7%) were unable to complete ADLs. Seventeen patients (47.2%) had one-year follow-up data, and of these, six (35.3%) reported hearing loss, one (5.9%) reported seizures, six (35.3%) behavioral and cognitive deficits, and three (17.6%) were unable to complete ADLs.

Table 2

Delays greater than 6 hours from presentation to LP

Patient ID	Hours from presentation to LP	Cause of Delay
2	8	History of meningitis
3	8	Misdiagnosed (Percocet overdose, otitis media).
7	7	Misdiagnosed (seizure and developmental delay)
8	8	Misdiagnosed (stroke and drug toxicity due to opioid, cocaine and heroin abuse)
9	50	Misdiagnosed (alcohol withdrawal)
10	8	Unknown.
23	11	History of meningitis. Started on antibiotics before LP due to rapidly deteriorating status and LP deferred until neuro consult.
25	27	Misdiagnosed (injury due to physical altercation)
27	11	Misdiagnosed (symptoms related to recent influenza)
28	17	Unable to give complete history due to pain and altered mental status.
29	14	Misdiagnosed (complicated by new diagnosis of pituitary adenoma in ED)
30	8	Misdiagnosed and hesitance of family to consent for LP (symptoms initially thought to be from recent infection and lymphatic malformation)
37	7	Misdiagnosed (gastrointestinal illness)
39	9	Healthcare proxy did not consent to LP
40	14	Deferred due to concern for cerebral edema
41	7	Misdiagnosed (non-specific leg pain)
43	8	Unable to give complete history due to altered mental status

Discussion

This retrospective descriptive study identified time to LP and diagnosis in CABM presenting to three tertiary medical centers, and identify contributing factors to misdiagnosis, management delays, and poor outcome. The rates of residual hearing loss, seizure, behavioral and cognitive deficits, and ability to complete ADLs in this cohort remained consistent with those found in past studies (Thigpen et al[9], Oordt-

Speets[4], van de Beek et al[10], Zoons et al[11], Worsøe et al[12], Brouwer et al[13]). Overall survival rates, as well as the rates of most common sequelae of BM, were also comparable to those in previous studies.

This study reports a delay in time to LP and to antibiotic administration as shown by previous studies (Proulx et al[6], Auburtin et al[5]). Initial misdiagnosis accounted for all delays of three hours or more from presentation to antibiotic treatment and delays from presentation to LP. Some LPs were deferred due to concern for cerebral edema or patient hesitancy to consent to LP.

In this study, the median time from presentation to LP was eight hours, and the median time from presentation to appropriate antibiotic administration was four hours as compared to estimates of one to two hours in prior similar cohorts (Miner et al[14], Bodilson et al[15]). Importantly, while overall time from presentation to antibiotic administration was longer in this cohort than prior similar cohorts, individuals who were not initially misdiagnosed were administered antibiotics in two hours or less–similar to previously published treatment times. This disparity in the current cohort suggests that taking steps to prevent misdiagnoses can significantly reduce delays to LP and antibiotic administration, thereby likely improving clinical outcomes. Contributing factors to misdiagnosis in this study include initial presentation to an outpatient clinic and a preceding or coinciding illness veiling CABM.

This study has several important limitations. Firstly, the ICD discharge codes used to identify potential cases may not include all cases of CABM. This study also lacks detailed symptomology at presentation, which could possibly identify factors associated with misdiagnoses and diagnostic delays. Further, the retrospective design relies on data obtained through EMRs which is subject to the availability and completeness of user entries. Lastly, the study has a small sample size and focuses only on three sites in NYC. However, this study capitalized on the sociodemographic diversity of the NYC patient sample that uniquely contributes to the epidemiological characterization of CABM. This study also provides insight into how tertiary NYC EDs and hospitals manage CABM cases. Our dataset provides timestamped data for many clinical and demographic variables, enabling a more thorough exploration of the epidemiological associations underpinning diagnostic and treatment delays.

Conclusions

Future studies are needed to investigate contributing factors of diagnostic and treatment delays such as detailed clinical symptomology, language and literacy barriers, and geographic proximity/physical accessibility to care facilities that may contribute to poor prognosis. Increased awareness of the ramifications of delayed antibiotic treatment in mortality and permanent neurological sequelae can offer care providers better qualitative metrics by which to triage vulnerable cases. As the epidemiological profile of BM continues to evolve by virtue of antibiotic resistant strains and serotype replacement, it is essential to optimize preventative, diagnostic and therapeutic measures to reduce mortality and increase quality of life for survivors.

Declarations

Ethics approval and consent to participate: This study was approved by the Columbia University Irving Medical Center Institutional Review Board (CUIMC IRB, New York, NY), Icahn School of Medicine at Mount Sinai IRB (New York, NY), and Weill Cornell Medical Center IRB (New York, NY). Waivers of consent were granted to all sites by their respective IRBs.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: Jacqueline Gofshteyn, is supported by the NIH/NINDS NSADA-K12 Career Development Award (NS5250799523). Kiran Thakur is supported by the **National Institute of Health, NINDS K23 NS105935-01** and NIH/NICHD 1R01HD074944-01A1

Authors' contributions: SDT collected and extracted and statistically analyzed data, and was a major contributor in writing the manuscript. MD collected and extracted and statistically analyzed data, and contributed to writing and editing of the manuscript. CYK contributed to the writing and revision of the manuscript. JVK statistically analyzed the data. NL collected and extracted the data. MH collected and extracted the data. EMS reviewed and revised the manuscript. BG collected the data, and reviewed and revised the manuscript. SSM conceptualized and designed the study, collected data, reviewed and revised the manuscript. DW reviewed and revised the manuscript. JSG reviewed and revised the manuscript. AKY reviewed and revised the manuscript. KTT conceptualized and designed the study, wrote the initial draft, reviewed and revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements: The authors thank Yifei Sun, PhD for her contributions to statistical data analysis and Ugoada C. Ofoezie, MD, MS, for her review of the manuscript.

References

1. Glimaker M, Johansson B, Grindborg O, Bottai M, Lindquist L, & Sjolin J. Adult bacterial meningitis: Earlier treatment and improved outcome following guideline revision promoting prompt lumbar puncture. Clin Infect Dis. 2015; 60(8):1162-9. doi:10.1093/cid/civ011

2. Cohn AC, MacNeil JR, Harrison LH, Hatcher C, Theodore J, Schmidt M, et al. Changes in Neisseria meningitidis disease epidemiology in the United States, 1998–2007: implications for prevention of meningococcal disease. Clin Infect Dis. 2010; 50(2):184–91. doi: 10.1086/649209

3. World Health Orgnization. Meningococcal meningitis; Facts sheet 2017. http://www.who.int/mediacentre/factsheets/fs141/en/. November 9, 2017. Updated December 2017. Accessed April 20, 2019.

4. Oordt-Speets AM, Bolijn R, van Hoorn RC, Bhavsar A, Kyaw MH. Global etiology of bacterial meningitis: A systematic review and meta-analysis. PLoS One. 2018; 13(6):e0198772. doi:10.1371/journal.pone.0198772

5. Auburtin M, Wolff M, Charpentier J, Varon E, et al. Detrimental role of delayed antibiotic administration and penicillin-nonsusceptible strains in adult intensive care unit patients with pneumococcal meningitis: The PNEUMOREA prospective multicenter study. Crit Care Med. 2006; 34(11):2758-2765. doi:10.1097/01.CCM.0000239434.26669.65

6. Proulx N, Fréchette D, Toye B, Chan J, Kravcik S. Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. QJM. 2005; 98(4):291-298. doi:10.1093/qjmed/hci047

7. RStudio Team. RStudio: Integrated Development for R [Computer software]. 2015. RStudio Inc., Boston, Massachusetts. http://www.rstudio.com/

8. SAS Institute Inc [Computer software]. 2013, Cary, North Carolina, USA

9. Thigpen MC, Whitney CG, Messonier NE, et al. Bacterial meningitis in the United States, 1998-2007. N Engl J Med. 2011; 364(21):2016-2025. doi:10.1056/NEJMoa1005384

10. van de Beek D, de Gans J, Tunkel AR, Wijdicks EF. Community-acquired bacterial meningitis in adults. N Engl J Med. 2006; 354(1):44-53. doi: 10.1056/NEJMra052116

11. Zoons E, Weisfelt M, de Gans J, et al. Seizures in adults with bacterial meningitis. Neurology. 2008; 70(22 Pt 2):2109-15. doi:10.1212/01.wnl.0000288178.91614.5d

12. Worsøe L, Caye-Thomasen P, Brandt CT, Thomsen J, Østergaard C. Factors associated with the occurrence of hearing loss after pneumococcal meningitis. Clin Infect Dis. 2010; 51(8): 917–924. doi: 10.1086/656409

13. Brouwer MC, Tunkel AR, van de Beek D. (2010). Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clin Microbiol Rev. 2010;23(3):467-492. doi:10.1128/CMR.00070-09

14. Miner JR, Heegaard W, Mapes A, Biros M. Presentation, time to antibiotics, and mortality of patients with bacterial meningitis at an urban county medical center. J Emerg Med. 2001; 21(4):387-392. doi:10.1016/s0736-4679(01)00407-3

15. Bodilsen J, Dalager-Pedersen M, Schønheyder HC, Nielsen H. Time to antibiotic therapy and outcome in bacterial meningitis: a Danish population-based cohort study. BMC Infect Dis. 2016;16:392. doi: 10.1186/s12879-016-1711-z.

16. Hsu HE, Shutt KA, Moore MR, et al. (2009). Effect of pneumococcal conjugate vaccine on pneumococcal meningitis. N Engl J Med. 2009; 360(3):244-256. doi:10.1056/NEJMoa0800836

17. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein–polysaccharide conjugate vaccine. N Engl J Med.2003; 348(18):1737-1746. doi:10.1056/NEJMoa022823

18. Data from NYC DOHMH. EpiQuery (meningitis, bacterial). https://a816-healthpsi.nyc.gov/epiquery/. Accessed April 10, 2019.

Abbreviations

CABM	Community Acquired Bacterial Meningitis
CUIMC	Columbia University Irving Medical Center
CHONY	Children's Hospital of New York
EMR	Electronic Medical Records
CSF	Cerebrospinal Fluid
PCR	Polymerase Chain Reaction
BM	Bacterial Meningitis
ICU	Intensive Care Unit
ED	Emergency Department
LP	Lumbar Puncture
CNS	Central Nervous System
GCS	Glasgow Coma Score
GOS	Glasgow Outcome Score
ADL	Ability to complete tasks of Daily Living
OSH	Outside Hospital