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Investigation of the Selection and Timing of Pharmacological Therapy in Community-Acquired Bacterial Meningitis

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Investigation of the Selection and Timing of Pharmacological Therapy in Community-Acquired Bacterial Meningitis

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ABSTRACT

Background: Bacterial meningitis is responsible for significant morbidity and mortality, but early appropriate therapy is expected to improve outcomes. National treatment guidelines were published in 2004, but no assessment of their utilization in the U.S. has been reported.

Objectives: To measure adherence to meningitis treatment guidelines and describe patient outcomes in relation to recommended antibiotic and dexamethasone use.

Methods: Retrospective chart reviews were performed on patients with bacterial meningitis who presented to emergency departments at two community teaching hospitals. Timing and appropriateness of antibiotic and dexamethasone use were assessed according to national guidelines. Patient outcomes of mortality, length of hospitalization, and neurological complications were analyzed based on therapies received.

Results: A total of 161 cases were identified; 38 met inclusion criteria. Recommended antibiotic regimens were administered to 52.6% of patients, while 26.3% received that regimen within eight hours. Dexamethasone was used in 44.7% of patients, but was administered prior to antibiotics in only 10.5% of cases. Mortality was numerically lower with recommended antibiotic therapy but did not reach statistical significance (5.0% versus 16.7%; $P = 0.33$). Median length of stay was eight days for patients who received recommended antibiotics and 11 days for those who did not ($P = 0.69$). One patient who received dexamethasone had a neurological complication at discharge compared with four patients not receiving dexamethasone (5.9% versus 19.0%, $P = 0.35$).

Conclusion: Current treatment guidelines provide clinicians with direction on optimal care for patients with bacterial meningitis, and an opportunity exists to improve implementation of these recommendations, which could improve patient outcomes.

Keywords: bacterial meningitis, antibiotic therapy, dexamethasone, community-acquired disease

INTRODUCTION

Bacterial meningitis remains a very lethal disease, accounting for more than 4,000 cases and 500 deaths annually in the United States.[1] The rate of occurrence has drastically decreased over the past few decades, due largely to the increased vaccination against common pathogens. A 31% reduction in incidence of bacterial meningitis was seen from 1998–1999 to 2006–2007; however, fatality rates remain high for the cases of bacterial meningitis that do occur, with an overall mortality rate of 14.3%.[1]

No prospective studies exist regarding the relationship of antibiotic timing with clinical outcomes in bacterial meningitis, but retrospective studies have suggested a correlation between antibiotic delay and unfavorable patient outcomes.[2–4] Therefore, the Infectious Diseases Society of America (IDSA) Practice Guidelines for the Management of Bacterial Meningitis indicate that patients with suspected bacterial meningitis should be treated as a "neurological emergency" and state that appropriate therapy should be initiated as soon as possible after the diagnosis is considered likely.[5]

The IDSA guidelines recommend using dexamethasone in adults with suspected or proven pneumococcal meningitis, and in infants and children with *Haemophilus influenzae* type b meningitis. It is also recommended that the initial dose be administered just prior to or concomitantly with the first antibiotic dose, but that it not be used in patients who have already received an antibiotic, as it is unlikely to improve outcomes if given after antibiotics.[2]

The purpose of this study was to examine how frequently patients presenting with community-acquired bacterial meningitis were administered guideline-recommended therapies of appropriate antibiotics and dexamethasone, and secondarily to examine the effects of early initiation of these therapies on patient outcomes of mortality and long-term neurological complications.

METHODS

Following approval of the institutional review board, patients were identified by ICD-9 codes 320.1–320.99 for bacterial meningitis at two community teaching hospitals licensed for approximately 500 patient beds each. Both facilities share a level 1 trauma designation and have comprehensive emergency departments (EDs), with one having a children's hospital. A retrospective review of electronic medical records and laboratory data was performed for all patients diagnosed from 2006 to 2011.

Patients were included, regardless of age, if they had a positive cerebrospinal fluid (CSF) culture or Gram's stain or alternatively had three of the following findings in their CSF: a) a white blood cell count of more than 1,000 cells/mL; b) more than 80% neutrophils; c) elevated protein (more than

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Table 1 Recommended Antibiotics Based on Patient Age[5]

Age	Recommended Antibiotic Regimen
< 1 month	Ampicillin + cefotaxime, OR ampicillin + aminoglycoside
1 month–50 years	Vancomycin + third-generation cephalosporin*
> 50 years	Vanocmycin + third-generation cephalosporin* + ampicillin

* Cefotaxime or ceftriaxone.

100 mg/dL); d) decreased glucose (less than 40 mg/dL or CSF:serum glucose ratio less than 0.4) with at least one of the typical meningitis symptoms of nuchal rigidity, altered mental status, fever, or severe headache.

Patients were excluded if they had a potential nosocomial infection, defined as CSF culture obtained more than 48 hours after presentation, confirmed viral or fungal meningitis, CSF shunt, penetrating head trauma, history of neurosurgery, multiple admissions for bacterial meningitis (only the first episode was included), previously known neurological disorder, transfer from another hospital, cardiac or respiratory arrest upon arrival, or incomplete data.

Treatments were assessed for appropriate selection of antibiotics and use of dexamethasone. Appropriate antibiotics were defined as one of the recommended regimens for empiric treatment based on the patient's age according to IDSA practice guidelines (Table 1). Alternative therapies were deemed appropriate if the patient had a documented allergy that warranted use of an alternative antibiotic listed in the IDSA guidelines.[5] The time between presentation to the ED and administration of each antibiotic was evaluated, with a cut point of eight hours after arrival to the ED. Dexamethasone use was considered to be appropriate if administration of any dose occurred prior to or concomitantly with initial antibiotics. Mortality and neurological complications were assessed from discharge summaries and subsequent patient records when available, with a maximum follow-up of six years. Long-term neurological complications were defined as hearing loss, delayed development, or any neurological abnormalities documented as likely resulting from meningitis. Clinical outcomes of mortality and neurological complications were compared for groups of patients who did or did not receive timely guideline-recommended therapies. Patients who survived to discharge were analyzed for length of hospitalization.

Statistical analysis was performed with Excel 2010 (Microsoft, Redmond, Washington) and GraphPad QuickCalcs (GraphPad Software, Inc., La Jolla, California). Fisher's exact test was used to compare mortality and neurological complications. Length of hospitalization was analyzed using the Student's *t*-test for normally distributed data and Wilcoxon rank sum test for data not normally distributed. Two-sided alpha was set *a priori* at 0.05 for all analyses.

RESULTS

A total of 161 diagnoses for bacterial meningitis occurred in the five years studied; 95 cases were at one institution and 66 at the other. Thirty-eight patients met inclusion criteria, 19 at each site. Demographic information of included patients is displayed in Table 2. A majority of excluded patients were excluded due to being transferred from outside facilities, prohibiting analysis of initial pharmacological treatments. Table 3 describes microbiology results of included patients.

Table 2 Patient Demographics (n = 38)

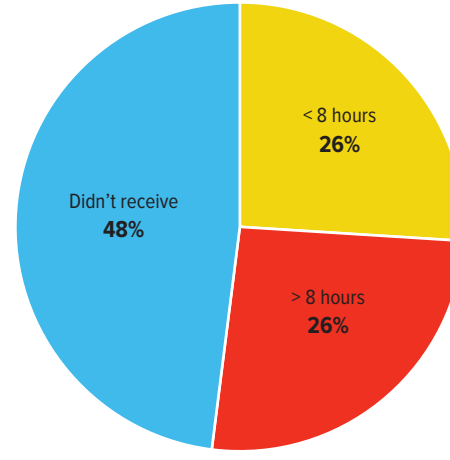
Male	63.2%
Age, mean (range)	46.5 years (11 days–77 years)
< 1 month	18.4%
1 month–50 years	21.1%
≥ 50 years	60.5%

Appropriate antibiotic selection and administration are displayed in Figure 1. Appropriate antibiotic administration, regardless of timing, occurred in 52.6% of patients. Omission of ampicillin was the most common deviation from the guidelines, occurring in 36.8% of patients, all more than 50 years of age. Other deviations from the guidelines included failure to receive a third-generation cephalosporin (10.5%) and failure to receive vancomycin (5.3%) when patients should have, according to IDSA guidelines. Two patients had more than one reason why antibiotic selection varied from guideline recommendations.

All patients received at least one recommended antibiotic. The median time between presentation to the ED and administration of the first antibiotic was 4.2 hours; the second antibiotic was 7.0 hours (n = 32); and the entire guideline-recommended regimen, regardless of the number of needed antibiotics, was 8.6 hours (n = 20). Dexamethasone was used in 44.7% of patients, with 10.5% receiving a dose prior to the first antibiotic as recommended by the guidelines.

Mortality rates according to appropriate antibiotic selection are displayed in Figure 2. No fatalities were observed among the patients who received a recommended antibiotic regimen within eight hours of arrival (n = 10). The median length of hospital stay was eight days (interquartile range [IQR], 6.3–12.8 days) for patients who received appropriate antibiotics within eight hours of arrival compared to 11 days

Figure 1 Administration of Guideline-Recommended Antibiotics



(IQR, 5.0–16.8 days) for those who did not ($P = 0.69$).

The use of dexamethasone and rate of neurological complications are displayed in Figure 3. No neurological complications were seen in the patients who received dexamethasone prior or concurrent to the first antibiotic (n = 4). Neurological complications were seen in two adults and three neonatal patients. One neonate was administered hydrocortisone one hour after antibiotics, while the other four patients did not receive corticosteroids at any time. The adults with neurological complications grew *Streptococcus pneumoniae* and group B *Streptococcus*, while the neonatal patients grew group B *Streptococcus* (two patients) and *Escherichia coli*. The most common neurological complication was hearing loss (n = 4), with both delayed development and cerebral palsy later documented in one neonatal patient.

Table 3 Cerebrospinal Fluid Culture Microbiology Results

Organism	Patient Age			Total
	< 1 month	1 month–50 years	> 50 years	
Streptococcus pneumoniae		1	11	12
Escherichia coli	2		2	4
Group B *Streptococcus*	2		1	3
Staphylococcus aureus		1	2	3
Coagulase-negative *Staphylococcus*	1			1
Viridans group *Streptococcus*		1		1
Streptococcus bovis	1			1
Enterobacter species			1	1
No organism	1	5	6	12
Total	7	8	23	38

DISCUSSION

While treatment guidelines for the management of bacterial meningitis have been widely available since 2004, new data have validated their recommendations. To our knowledge, this is the first study in the U.S. that assesses their adoption into practice.

Timing of antibiotics is an important discussion. Although no prospective studies exist regarding the relationship of antibiotic timing with clinical outcomes in bacterial meningitis, several retrospective studies have suggested a correlation between antibiotic timing and patient outcomes. A retrospective study of 305 patients showed that those who received an antibiotic prior to admission had a 1.9% mortality rate, compared to 12% in those with delayed treatment.[2] A similar study of 171 cases of bacterial meningitis showed that patients who received antibiotics in the ED had a 10% mortality rate, compared to 29% in patients who did not receive antibiotics in the ED.[3] Additionally, a multicenter retrospective study revealed that progression in disease severity before antibiotic administration was associated with significantly higher rates of adverse outcomes.[4] These findings substantiate the importance of early antibiotic administration.

It is also relevant to discuss the analysis of time to antibiotics performed in this study. Practice guidelines from IDSA recommend that antibiotics be initiated "as soon as possible after the diagnosis is considered to be likely." Eight hours was chosen as the cutoff for time to administration based on several factors, including knowledge of the average duration of stay in our EDs and that many patients receive computed tomography studies prior to lumbar puncture. This time frame of eight hours has also been associated with improved outcomes in pneumonia patients and was familiar to prescribers due to previous use in

Figure 2 Mortality Rate According To Antibiotic Administration

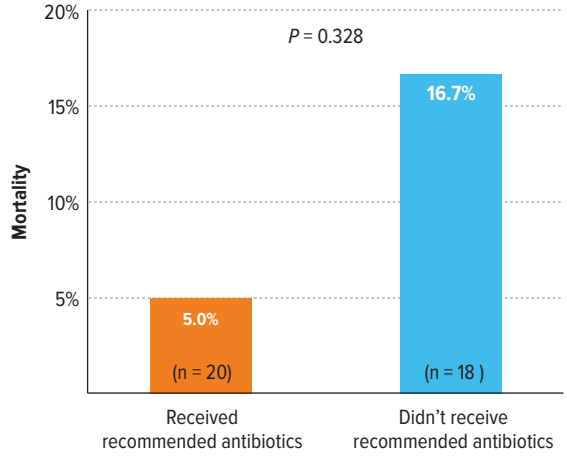
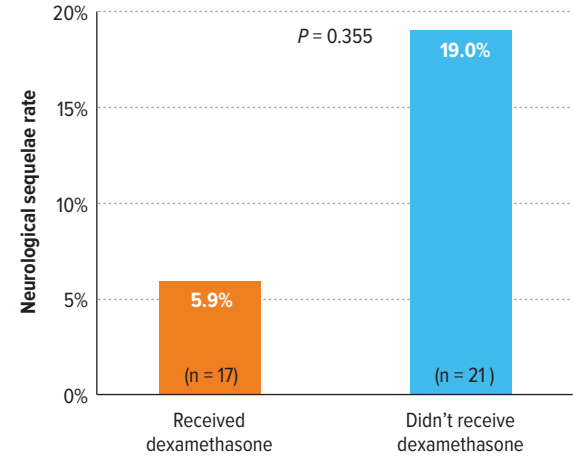


Figure 3 Long-Term Neurological Consequences According to Dexamethasone Administration



quality measures.[6] The authors feel that this time frame was a generous cutoff for a condition as serious as meningitis. While 26.3% of patients had recommended antibiotics initiated within eight hours, changing the cut point to six hours or 12 hours would have resulted in 18.4% and 31.5% receiving recommended antibiotics, respectively, showing that, regardless of time point used, the findings are concerning. While the exact cause for the delay in treatment is not clear from available data, the fact that extending the cut point from eight hours to 12 hours had little effect on the number of patients meeting the measure suggests that it was unlikely to have been caused by delays in the preparation and delivery of antibiotics.

Another concerning finding was the low utilization of dexamethasone. There have been numerous studies of dexamethasone use in bacterial meningitis, several of which have shown a benefit. A prospective, placebo-controlled study showed that dexamethasone in adults with bacterial meningitis reduced unfavorable outcomes from 25% to 15% and mortality from 15% to 7%.[7] In the subset of patients with pneumococcal disease, dexamethasone significantly reduced unfavorable outcomes from 52% to 26% and mortality from 34% to 14%.[7] Based on these data, dexamethasone use for pneumococcal meningitis in the Netherlands increased from 3% in 1998–2002 to 84% in 2006–2009, which showed a reduction in mortality from 30% to 20% and hearing loss from 22% to 12%, while unfavorable outcomes (Glasgow Coma Score less than 5 at discharge) decreased from 50% to 39%.[8] More recently, long-term survival was confirmed to increase from 67% to 78% in patients receiving dexamethasone.[9] Evidence also supports dexamethasone use in infants and children with meningitis caused by *H. influenzae* type b.[10] Therefore, giving dexamethasone empirically is recommended for patients with suspected meningitis because it is not possible to safely determine the causative organism before administering antibiotics at the time of presentation.[5] In the present study, 12 adults grew *S. pneumoniae*, only two of whom (12.6%) received adjunctive dexamethasone prior to antibiotics. There were no confirmed cases of *H. influenzae* type b in infants and children, so dexamethasone use in this population may not have been beneficial.

Timely treatment for community-acquired bacterial meningitis is important because early initiation of proper antibiotics has the potential to reduce mortality, and dexamethasone use has been proven to reduce neurological complications in select populations. Previous assessments of clinical practices have been reported by three European institutions, each having higher rates of adherence to guidelines than the current study, but all showing significant room for improvement.[11–13] The overall mortality rate observed in this study, however, was slightly lower than what has been seen in previous studies. This may have been due to the high number of patients excluded because of transfer from other facilities.

In our study, patients who received antibiotics within eight hours of arrival had the numerically lowest mortality rate and shortest length of stay; however, the results did not reach statistical significance, likely due to the small sample size. Additionally, no long-term complications were observed in patients who received dexamethasone prior or concurrent to the first antibiotic dose.

Although results of this study did not reach statistical significance, they are consistent with larger trials and are meaningful because they may reflect current U.S. practice patterns that have been unpublished until now. Therefore, it is necessary to find ways to ensure stricter adherence to guideline recommendations in an attempt to decrease morbidity and mortality in these patients.

One solution to this problem of delayed antimicrobial therapy may be the implementation of standardized order sets for suspected meningitis. Recognizing this, the studied institutions have cooperatively developed meningitis treatment protocols and have subsequently implemented them into computerized prescriber order-entry systems. Additionally, they are also working with outlying referral hospitals to improve processes at these facilities. Both of the medical centers involved in this study have assigned pharmacists to review orders and assist prescribers with treatment decisions in the ED, starting shortly after the end of our data.

The greatest limitations of this study are the small sample size and retrospective design. While trends in data are telling, small sample size may have contributed to II error, the failure to reject a false null hypothesis (a "false negative"). Even though 161 cases of meningitis were treated at these medical centers during the time evaluated, a majority of patients could not be included in this study because they were transferred from other hospitals, which created incomplete data sets regarding timing and administration of therapy. Additionally, many of the patients with ICD-9 codes for bacterial meningitis had been diagnosed based on clinical symptoms, but lab results did not meet study criteria. Inclusion of these patients would have created a larger sample size, but integrity of the data could have been compromised because some of these cases may not actually have been bacterial meningitis. The recognition of long-term neurological complications relied on documentation of such in the patients' electronic medical records within the health system, but confirmation of specific testing could not be verified; therefore, this study may have underestimated the true prevalence.

Although clear treatment recommendations for a variety of diseases exist, analyses have revealed adherence for many practice guidelines to be low.[14] Careful ongoing review provides opportunities to identify and correct potential shortcomings at the point of prescribing. Our study has shown limited adherence to practice guidelines for bacterial meningitis and allowed us to make interventions in an attempt to ameliorate this problem. We are hopeful that implementing the new meningitis treatment protocol across multiple medical facilities, integrating it into computerized prescriber order-entry systems, and making a clinical pharmacist available at the point of prescribing will improve adherence to guideline recommendations. Based on our results and previous literature, this has the potential to reduce mortality and prevent neurological sequelae in patients with meningitis.

CONCLUSION

Our data show that many patients presenting to EDs with community-acquired bacterial meningitis do not receive recommended antibiotics promptly after presentation or appropriate administration of dexamethasone. These therapies have previously been shown to result in more favorable patient

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outcomes ranging from less hearing loss to lower mortality rates. Therefore, efforts must be made to improve the adherence with treatment guidelines for bacterial meningitis in hopes of improving patient outcomes.

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CMS to Test Enhanced MTM Model

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approach. Instead, it wants the CMS to focus on adopting proactive means of identifying at-risk beneficiaries, such as lock-in programs and expanding access to state prescription drug monitoring program data to health plans.

Of course, at-risk beneficiaries are also the targets of the EMTM model, except that those being pinpointed will have costly medical conditions, such as diabetes and coronary heart disease. If Part D plans are able to better find and help those on the cusp or in the throes of opioid addiction—people often headed for bad outcomes—and also establish higher-value MTM programs, they will be on their way to a new era where "value" becomes a Part D watchword.

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Dosage and Administration: Inflectra is administered by intravenous infusion over a period of at least two hours. Dosing varies with indication and patient weight:

CD: 5 mg/kg at zero, two, and six weeks, then every eight weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response.

Pediatric CD, UC, PsA, and plaque psoriasis: 5 mg/kg at zero, two, and six weeks, then every eight weeks.

RA: In conjunction with methotrexate, 3 mg/kg at zero, two, and six weeks, then every eight weeks. Some patients may benefit from increasing the dose to 10 mg/kg or treating as often as every four weeks.

AS: 5 mg/kg at zero, two, and six weeks, then every six weeks.

Commentary: The approval of Inflectra was based on the review of evidence that included structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamics data, clinical immunogenicity data, and other clinical safety and effectiveness data that demonstrates Inflectra is biosimilar to Remicade. The most common side effects of Inflectra include respiratory infections, headache, coughing, and stomach pain. Infusion reactions can occur up to two hours postinfusion, with symptoms including fever, chills, chest pain, hypotension or hypertension, shortness of breath, rash, and/or itching.

Sources: Celltrion, Inc.; Inflectra prescribing information ■