

# Corticosteroids and Mortality in Children With Bacterial Meningitis

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**A**DJUVANT CORTICOSTEROID therapy reduces hearing loss in children with meningitis caused by *Haemophilus influenzae* type b (Hib). However, the epidemiology of bacterial meningitis has changed dramatically following the licensure and widespread use of vaccines against Hib in 1985 and *Streptococcus pneumoniae* in 2000. The current benefit of adjuvant corticosteroids for the treatment of bacterial meningitis in children remains unclear. Guidelines from the Committee on Infectious Disease of the American Academy of Pediatrics acknowledge this uncertainty and state that for infants and children aged 6 weeks or older, “adjunctive therapy with dexamethasone may be considered after weighing the potential benefits and risks.”<sup>1</sup> Adjuvant corticosteroids, when used, should be administered with or shortly before the first dose of antimicrobial therapy.<sup>1</sup>

Antimicrobial-induced bacteriolysis leads to inflammation and cerebral edema. The beneficial effects of corticosteroids are attributed to attenuation of this inflammatory response.<sup>2,3</sup> Concerns over the use of corticosteroids relate to the potential for decreased cerebrospinal fluid (CSF) penetration of antibiotics and potential adverse effects of corticosteroids, namely gastrointestinal bleeding.<sup>4</sup> Other concerns with corticosteroid use include the potential to mask antimicrobial failure by preventing a secondary fever.<sup>5</sup>

**Context** In adults, adjuvant corticosteroids significantly reduce mortality associated with bacterial meningitis; however, in children, studies reveal conflicting results.

**Objective** To determine the association between adjuvant corticosteroids and clinical outcomes in children with bacterial meningitis.

**Design, Setting, and Patients** A retrospective cohort study conducted between January 1, 2001, and December 31, 2006, of 2780 children discharged with bacterial meningitis as their primary diagnosis from 27 tertiary care children’s hospitals located in 18 US states and the District of Columbia that provide data to the Pediatric Health Information System’s administrative database.

**Main Outcome Measures** Propensity scores, constructed using patient demographics and markers of illness severity at presentation, were used to determine each child’s likelihood of receiving adjuvant corticosteroids. Primary outcomes of interest, time to death and time to hospital discharge, were analyzed by using propensity-adjusted Cox proportional hazards regression models stratified by age categories.

**Results** The median age was 9 months (interquartile range, 0-6 years); 57% of the patients were males. *Streptococcus pneumoniae* was the most commonly identified cause of meningitis. Adjuvant corticosteroids were administered to 248 children (8.9%). The overall mortality rate was 4.2% (95% confidence interval [CI], 3.5%-5.0%), and cumulative incidences were 2.2% and 3.1% at 7 days and 28 days, respectively, after admission. Adjuvant corticosteroids did not reduce mortality, regardless of age (children <1 year: hazard ratio [HR], 1.09; 95% CI, 0.53-2.24; 1-5 years: HR, 1.28; 95% CI, 0.59-2.78; and >5 years: HR, 0.92; 95% CI, 0.38-2.25). Adjuvant corticosteroids were also not associated with time to hospital discharge. In subgroup analyses, the results did not change in either children identified with pneumococcal or meningococcal meningitis or children with a cerebrospinal fluid culture performed at the admitting hospital.

**Conclusion** In this multicenter observational study of children with bacterial meningitis, adjuvant corticosteroid therapy was not associated with time to death or time to hospital discharge.

JAMA. 2008;299(17):2048-2055

www.jama.com

In adults, adjuvant corticosteroids decrease mortality in patients with bacterial meningitis, with the greatest benefit occurring in the subset of patients with pneumococcal meningitis.<sup>6,7</sup> In neonates and children, the effect of corticosteroids on mortality is controver-

sial. Only 1 small clinical trial<sup>8</sup> specifically evaluated corticosteroids in neonates; however, the study was not included in a large Cochrane review. The results of that study of neonates by Daoud et al<sup>8</sup> showed no difference in mortality between treatment and con-

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tol groups. A retrospective study of 120 children with pneumococcal meningitis conducted between 1994 and 1999 found that adjuvant corticosteroid use was associated with a lower odds of death in adjusted analysis.<sup>9</sup> However, a subsequent Cochrane review<sup>10</sup> of randomized controlled trials from 1969 to 2006 found no significant difference in mortality in children younger than 16 years who received corticosteroids compared with those who did not receive corticosteroids for all causative organisms, although the overall mortality rate was lower than previously reported in some of the studies. Furthermore, few of these studies were conducted in the United States.

In a multicenter randomized controlled trial<sup>11</sup> conducted in Latin America not included in the Cochrane review, adjuvant corticosteroids had no effect on mortality in children aged 2 months to 16 years. However, the study was performed in areas where Hib accounted for most cases of meningitis. Also, in contrast with previous work, the study found no protection against hearing loss in the 54 children with Hib meningitis who received adjuvant corticosteroids compared with controls.<sup>11</sup> A more recent randomized trial<sup>7</sup> in Vietnam found that adjuvant corticosteroids decreased overall mortality in those individuals with culture-confirmed bacterial meningitis. The study included adults and adolescents; however, the results were not stratified by age.<sup>7</sup>

The goal of our study was to determine the effect of adjuvant corticosteroid therapy on mortality and length of hospitalization in children with bacterial meningitis treated at tertiary care children's hospitals in areas where Hib meningitis is no longer prevalent.

## METHODS

### Data Source

Data for this retrospective cohort study were obtained from the Pediatric Health Information System (PHIS), a national administrative database containing resource utilization data from 27 freestanding, tertiary care children's hospitals. Participating PHIS hospitals account for 20%

of all tertiary care general (rather than subspecialty) children's hospitals, which are located in 18 US states and the District of Columbia; no more than 1 hospital is present in a specific region. These hospitals are affiliated with the Child Health Corporation of America (Shawnee Mission, Kansas), a business alliance of children's hospitals.

Data quality and reliability are ensured through a joint effort between the Child Health Corporation of America and participating hospitals. Systematic monitoring occurs on an ongoing basis to ensure data quality. Specific processes include bimonthly coding consensus meetings, coding consistency reviews, and quarterly data quality reports. For the purposes of external benchmarking, participating hospitals provide discharge data including patient demographics, diagnoses, and procedures. Total hospital charges are reported in the PHIS database and adjusted for hospital location using the Centers for Medicare & Medicaid price/wage index. Data were deidentified before inclusion in the database; however, encrypted medical record numbers allow for tracking individual patients across hospital admissions. The protocol for the conduct of this study was reviewed and approved by The Children's Hospital of Philadelphia Committees for the Protection of Human Subjects with a waiver of informed consent.

### Study Patients

Children younger than 18 years with bacterial meningitis were eligible for inclusion if they were discharged from any of the 27 hospitals between January 1, 2001, and December 31, 2006. Study participants discharged with bacterial meningitis as their primary diagnosis were identified in the PHIS database using *International Classification of Diseases, Ninth Revision (ICD-9)* discharge diagnosis codes. Adjuvant corticosteroids have not traditionally been used to treat children with ventricular shunt infections, because the presence of a shunt or subsequent placement of an external ventricular drain prevents

life-threatening increases in intracranial pressure. Therefore, patients with ventricular shunts before the episode of bacterial meningitis were excluded by using the following ICD-9 procedure codes: ventricular shunt replacement (02.42); incision of peritoneum (54.95); removal of ventricular shunts (02.43); and the ICD-9 discharge diagnosis code for mechanical complication of nervous system device, implant, and graft (996.2). If a study participant had more than 1 hospitalization with bacterial meningitis during the study period, only data from the first hospitalization were included.

### Study Definitions

Study participants were identified from the PHIS database by using ICD-9 codes for the primary diagnosis of bacterial meningitis (codes 036.0-036.1, 320.0-320.3, 320.7, 320.81-320.82, 320.89, and 320.9). Adjuvant corticosteroid therapy was defined as the receipt of dexamethasone, hydrocortisone, or methylprednisolone intravenously on the first day of hospitalization.<sup>12</sup> Comorbid conditions considered in the study included cancer (hematological and nonhematological), congenital heart disease, human immunodeficiency virus infection, prematurity, postoperative infection, and sickle cell disease. Anticonvulsants included diazepam, lorazepam, fosphenytoin, phenytoin, pentobarbital, phenobarbital, and valproate. Vasoactive infusions included dobutamine, dopamine, epinephrine, and norepinephrine. Race and ethnicity data of participants were reported by either the participants or their parents.

### Outcome Measures

The main outcome measures of interest in our study were time to death and time to hospital discharge, and the main exposure of interest was the use of adjuvant corticosteroid therapy within the first 24 hours of hospital admission.

### Statistical Analysis

We conducted unadjusted and adjusted analyses of the associations be-

tween adjuvant corticosteroid therapy and time to death and time to hospital discharge. Unadjusted analyses included median time to outcome, Kaplan-Meier curves, and the log-rank statistic. Propensity-adjusted Cox proportional hazards regression models were used to adjust for potential confounding by observed baseline confounders because the number of covariates within our study was large relative to the number of outcomes, a situation in which multivariate modeling may create unreliable estimates.<sup>13-16</sup> Propensity scores estimate the probability of receiving a specific treatment (in this case, adjuvant corticosteroids) given an observed set of confounders, aiming to control for measured confounders in the treatment and no treatment groups in an observational study.<sup>17,18</sup>

Accordingly, we created a propensity score using multivariate logistic regression to assess the likelihood of exposure to adjuvant corticosteroids. The model used sex, race, vancomycin use within the first 24 hours of admission, admission during enterovirus season (May-October) vs nonenterovirus season, and comorbid conditions as risk factors for receiving vs not receiving corticosteroids. Race was included in the propensity score because of its association with corticosteroid administration. To account for severity of illness, the propensity model also included the following variables if present on the first day of hospital admission: requirement for endotracheal intubation, intramuscular or parenteral anticonvulsant therapy, vasoactive infusions, and mannitol. The model's calculated C statistic was 0.749, which represents the predictive capacity of the model. The model provides a better estimate than expected by chance alone, but remains in a range that allows for little concern over nonoverlapping propensity score distributions between treatment and no treatment groups, making comparisons possible.<sup>19</sup>

In the analysis of our primary outcomes, we adjusted for a child's propensity score for adjuvant corticoste-

roid therapy in each of the models. Adjusting for propensity score provides similar estimates to matching for propensity score, while allowing for inclusion of all eligible patients rather than a subset of patients with matched scores.<sup>20,21</sup> Each model stratified the data by age category (<1 year, 1-5 years, and >5 years) because the most likely infecting organism varies depending on age<sup>22</sup> and corticosteroids appear to have a differential effect depending on the causative organism.<sup>6</sup> Propensity-adjusted Cox proportional hazards regression models were used to separately analyze time to death and time to hospital discharge. For time to death, discharged patients were treated as censored patients. Similarly, for time to hospital discharge, deaths were treated as censored. A global test of proportional hazards for the propensity-adjusted regression model was not significant and, therefore, for our primary analysis a single model was fit for each outcome.

The propensity scores were not equally distributed. When the propensity scores were stratified by quintiles, a greater proportion of patients receiving adjuvant corticosteroids were in the highest quintile and a greater proportion of patients not receiving adjuvant corticosteroids were in the lowest quintile of propensity score. To address this imbalance, we repeated the analysis while excluding patients in the highest and lowest quintiles for propensity score.

To address limitations of administrative data, several additional analyses were conducted. First, despite our attempts to adjust for severity of illness, which could lead to the differential receipt of corticosteroids (sicker patients may be more likely to receive corticosteroids), residual confounding by indication may exist. Therefore, we examined the relationship of corticosteroid use to hospital charges in a propensity-adjusted logistic regression model. If some residual confounding by indication were present, we would expect that those patients who received corticosteroids would have greater resource utilization reflecting a

greater intensity of care and a more severe hospital course.<sup>23</sup> High charges were explored using \$250 000 in total hospital charges (the approximate 90th percentile for charges across all hospitals) as the cutoff value.

Second, the sensitivity and specificity of ICD-9 codes in identifying all children with bacterial meningitis are not known. However, it is likely that ICD-9 codes for specific common causes of bacterial meningitis (*S pneumoniae* or *Neisseria meningitidis*), as used by previous investigators,<sup>24-26</sup> are more accurate than ICD-9 codes for other causes of bacterial meningitis. Therefore, we created a separate propensity-adjusted Cox proportional hazards regression model stratified by infecting organism.

Finally, only free-standing tertiary care children's hospitals are included in the PHIS database. Some children may have had lumbar punctures performed at other hospitals before transfer to these tertiary care facilities, potentially leading to inaccurate classification of corticosteroid receipt. To account for this possibility, we performed a propensity-adjusted Cox proportional hazards regression analysis while restricting the cohort to patients who had a hospital charge for CSF culture on the initial day of hospitalization, suggesting that meningitis was diagnosed at the tertiary care hospital. Additional analysis was performed in the subset of children with pneumococcal or meningococcal meningitis with charges for CSF culture.

The models for all the analyses were clustered by hospital to account for the increased variability due to clustering of individuals within hospitals. Modeling quadratic and cubic propensity scores did not reduce the point estimates by more than 2% in any model. Two-tailed  $P < .05$  was considered statistically significant. Actual  $P$  values and 95% confidence intervals (CIs) are reported. Data were analyzed by using Stata version 9.2 (Stata Corporation, College Station, Texas). Because 248 of 2780 patients (8.9%) with bacterial meningitis received adjuvant cortico-

steroids, we had 80% power ( $\alpha = .05$ ) to detect a 20% or greater change in the hazard ratio (HR) for mortality of those patients receiving corticosteroids compared with those not receiving corticosteroids.

## RESULTS

### Patient Characteristics

During the study period, there were 2780 discharges with bacterial meningitis. The characteristics of study patients are shown in TABLE 1. The mean age was 3.4 years (median, 9 months; interquartile range [IQR], 0-6 years). *Streptococcus pneumoniae* was the most commonly identified cause of meningitis. On the first day of hospital stay, 1084 children (39%) received vancomycin, 444 (16%) received anticonvulsant therapy, and 274 (9.9%) received vasoactive infusions. Endotracheal intubation was required in 176 children (6.3%) on the first day of admission.

### Corticosteroid Use

Adjuvant corticosteroids were administered to 248 children (8.9%) overall, with dexamethasone (administered to 75% of corticosteroid recipients) being the most commonly used corticosteroid. The percentage of patients receiving adjuvant corticosteroid therapy increased over time from a nadir of 5.8% in 2001 to a peak of 12.2% in 2006 ( $\chi^2$  test for trend,  $P = .004$ ). Adjuvant corticosteroid use varied by hospital. The median percentage of patients receiving steroids at any hospital was 7.5%, ranging from 0% to 36.8% (IQR, 3.7%-11.7%).

### Outcome Measures

The overall mortality rate was 4.2% (95% CI, 3.5%-5.0%); the cumulative mortality rates were 2.2% and 3.1% at 7 days and 28 days, respectively, after admission (TABLE 2). Twenty-three percent of total deaths occurred on the first day of hospitalization; approximately half of the total deaths occurred during the first week of hospitalization. In the subset of children with pneumococcal meningitis ( $n = 504$ ), 29% of deaths occurred on the first day of hos-

pitalization and 71% of deaths occurred during the first week of hospitalization. There were 15 deaths (6.0%) in children who received corticosteroids and 102 deaths (4.0%) in children who did not receive corticosteroids (relative risk, 1.50; 95% CI, 0.89-2.54). The Kaplan-Meier curve displaying the proportion of patients hospitalized surviving as a function of time stratified by corticosteroid receipt is shown in the FIGURE. The difference in time to death was not statistically significant (log-rank  $P = .57$ ). Propensity-adjusted Cox proportional hazards regression analysis

showed that adjuvant corticosteroids were not associated with death in any age category (TABLE 3).

The overall median (IQR) length of stay was 11 (7-20) days. The median (IQR) length of stay for children who received corticosteroids was 12 (7-21) days, while the median (IQR) length of stay for the children who did not receive corticosteroids was 10 (6-20) days. The Figure shows the Kaplan-Meier curve depicting the length of hospitalization as a function of time stratified by corticosteroid receipt; the unadjusted difference in time to hospital discharge was not statistically sig-

**Table 1.** Characteristics of Patients<sup>a</sup>

Characteristics	No. (%) of Patients		
	Corticosteroid Treatment (n = 248)	No Corticosteroid Treatment (n = 2532)	Overall (N = 2780)
Age category, y			
<1	96 (38.7)	1371 (54.2)	1467 (52.3)
1-5	69 (27.8)	531 (21.0)	600 (21.6)
>5	83 (33.5)	630 (24.9)	713 (25.7)
Race/ethnicity <sup>b</sup>			
Non-Hispanic white	148 (59.7)	1307 (51.6)	1455 (52.3)
Non-Hispanic black	26 (10.5)	531 (21.0)	557 (20.0)
Hispanic	20 (8.1)	334 (13.2)	354 (12.7)
Other	26 (10.5)	246 (9.7)	272 (9.8)
Missing	28 (11.3)	114 (4.5)	142 (5.1)
Sex			
Male	149 (60.1)	1434 (56.6)	1583 (56.9)
Female	99 (39.9)	1098 (43.4)	1197 (43.1)
Type of insurance			
Government	115 (46.4)	1299 (51.3)	1414 (50.9)
Nongovernment/other <sup>c</sup>	133 (53.6)	1233 (48.7)	1366 (49.1)
Infecting organism (ICD-9 codes)			
<i>Neisseria meningitidis</i> (036.0 or 036.1)	34 (13.7)	246 (9.7)	280 (10.1)
<i>Haemophilus influenzae</i> (320.0)	30 (12.1)	89 (3.5)	119 (4.3)
<i>Streptococcus pneumoniae</i> (320.1)	64 (25.8)	440 (17.4)	504 (18.1)
<i>Streptococcus</i> species (320.2)	32 (12.9)	244 (9.6)	276 (9.9)
<i>Staphylococcus</i> species (320.3)	35 (14.1)	346 (13.7)	381 (13.7)
Gram-negative bacteria (320.82)	17 (6.9)	296 (11.7)	313 (11.3)
Other specified bacteria (320.89)	6 (2.4)	66 (2.6)	72 (2.6)
Meningitis in diseases classified elsewhere (320.7)	3 (1.2)	53 (2.1)	56 (2.0)
Anaerobes (320.81)	0	11 (0.4)	11 (0.4)
Unspecified bacterium (bacterial NOS, purulent NOS, pyogenic NOS, suppurative NOS [320.9])	27 (10.9)	741 (29.3)	768 (27.6)

Abbreviations: ICD-9, International Classification of Diseases, Ninth Revision; NOS, not otherwise specified.

<sup>a</sup>Because of rounding, percentages may not total 100.

<sup>b</sup>Race/ethnicity data were reported by either the participants or their parents. Other races included Asian, Native American, and other. Race was classified as missing if it was not reported in the database.

<sup>c</sup>Other type of insurance refers to insurance status classified as self-pay, workers compensation, or other.

nificant (log-rank  $P = .57$ ). Length of hospital stay, analyzed as time to hospital discharge, was not associated with the administration of adjuvant corticosteroids for any age group in the propensity-adjusted Cox proportional hazards regression analysis (Table 3).

When patients in the lowest and highest quintiles of propensity scores were excluded, there remained no overall association between adjuvant corticosteroid use and time to death (HR, 1.18; 95% CI, 0.48-2.88) or time to hospital discharge (HR, 0.89; 95% CI, 0.78-

1.03) among the remaining patients ( $n = 1649$ ).

To determine whether residual confounding by indication was still present despite adjusting for propensity score, we evaluated total hospital charges. The overall mean billed charge was \$111 027 (median, \$38 926; IQR, \$19 853-\$90 385). The median charge for children who received corticosteroid treatment was \$63 361 (IQR, \$33 487-\$136 454), while the median charge for children who did not receive corticosteroid treatment was \$36 800 (IQR, \$19 164-\$85 838) (Wilcoxon rank sum

test,  $P < .001$ ). However, in the propensity-adjusted multivariate logistic regression analysis, there was no difference in high charges between children who received corticosteroid treatment and children who did not receive corticosteroid treatment in any age category (TABLE 4).

When the results were stratified by infecting organism, time to death between children receiving and not receiving corticosteroid treatment did not change in children with meningitis caused by either *S pneumoniae* ( $n = 504$ ) (HR, 0.53; 95% CI, 0.11-2.51) or *N meningitidis* ( $n = 280$ ) (HR, 1.39; 95% CI, 0.39-5.03). Time to hospital discharge was also not significantly different when stratified by organism for either *S pneumoniae* (HR, 1.03; 95% CI, 0.81-1.31) or *N meningitidis* (HR, 0.70; 95% CI, 0.42-1.19).

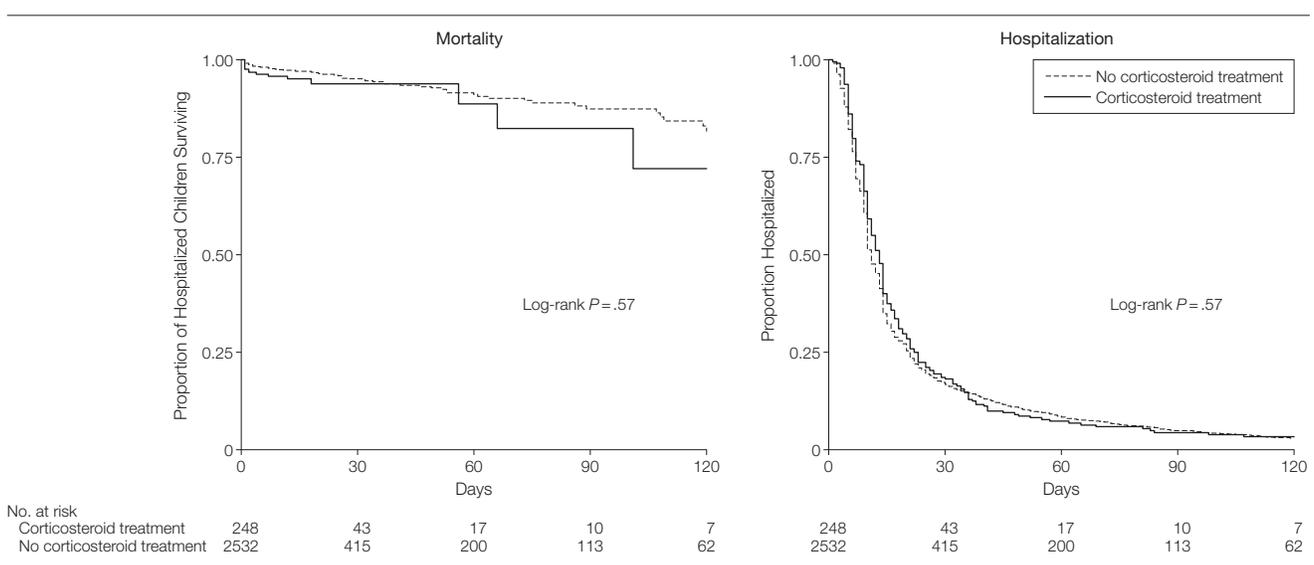
Onsite CSF cultures were performed on the first day of hospitalization for 1359 of 2780 children (48.9%) identified with bacterial meningitis. Of those children with CSF cultures, 199 (14.6%) were identified as having pneumococcal meningitis and 86 (6.3%) were identified as having meningococcal meningitis. There was no difference overall in time to death (HR, 0.69; 95% CI, 0.22-2.14) or time to hospital discharge (HR, 0.95; 95% CI, 0.79-

**Table 2.** Mortality Among Subgroups of Children With Bacterial Meningitis

	No./Total No. (%)		
	Corticosteroid Treatment	No Corticosteroid Treatment	Overall
Overall	15/248 (6.0)	102/2532 (4.0)	117/2780 (4.2)
Age category, y			
<1	7/96 (7.3)	59/1371 (4.3)	66/1467 (4.5)
1-5	4/69 (5.8)	17/531 (3.2)	21/600 (3.5)
>5	4/83 (4.8)	26/630 (4.1)	30/713 (4.2)
Organism			
<i>Streptococcus pneumoniae</i>	3/64 (4.7)	18/440 (4.1)	21/504 (4.2)
<i>Neisseria meningitidis</i>	3/34 (8.8)	11/246 (4.5)	14/280 (5.0)
<i>Haemophilus influenzae</i>	0/30 (0)	3/89 (3.4)	3/119 (2.5)
Other <sup>a</sup>	9/120 (7.5)	70/1757 (4.0)	79/1877 (4.2)

<sup>a</sup>Other organisms (International Classification of Diseases, Ninth Revision code) include *Streptococcus* species (320.2), *Staphylococcus* species (320.3), Gram-negative bacteria (320.82), other specified bacteria (320.89), meningitis in diseases classified elsewhere (320.7), anaerobes (320.81), and unspecified bacterium (320.9).

**Figure.** Probability of Death Among Hospitalized Patients and Proportion of Children Remaining Hospitalized, Stratified by Corticosteroid Administration



1.14) between those children receiving and not receiving adjuvant corticosteroid therapy. Among the subset of children with pneumococcal meningitis who had a CSF culture performed at the participating hospital, there were also no significant differences overall in time to death (HR, 0.31; 95% CI, 0.01-6.93) or time to hospital discharge (HR, 1.13; 95% CI, 0.85-1.49) between those receiving and not receiving corticosteroid treatment. Age-stratified analysis of this subset of patients with pneumococcal meningitis as well as any subgroup analysis of patients with meningococcal meningitis who had a CSF culture performed did not provide meaningful results due to the small number of deaths in these subsets.

## COMMENT

To our knowledge, this is the largest multicenter observational study conducted on bacterial meningitis and adjuvant corticosteroid therapy in children. Adjuvant corticosteroids were not associated with survival or length of hospital stay in children of any age or in the subset of children with pneumococcal or meningococcal meningitis. No difference in high hospital charges was found in the models comparing resource utilization, suggesting that our propensity score accounted for differences in severity of illness.

Our study demonstrates that adjuvant corticosteroids are not associated with a decrease in overall mortality in children with bacterial meningitis. A Cochrane review<sup>10</sup> of randomized controlled trials on adjuvant corticosteroids and bacterial meningitis conducted during 1969-2002 supports the findings of our study. In a subgroup analysis limited to children, the review found an overall mortality of approximately 13% in both the corticosteroid and placebo groups (relative risk, 0.99; 95% CI, 0.81-1.20).<sup>10</sup> The majority of studies included in the review had mortality rates of less than 5% except for several studies conducted in Africa and Pakistan where mortality rates ranged from 15% to 31%.<sup>10</sup> Also,

**Table 3.** Propensity-Adjusted Cox Proportional Hazards Regression Models for the Impact of Adjuvant Corticosteroids on Time to Death and Time to Hospital Discharge Stratified by Age Category (N = 2780)

	Age Category, y		
	<1	1-5	>5
Time to death			
Hazard ratio (95% CI)	1.09 (0.53-2.24)	1.28 (0.59-2.78)	0.92 (0.38-2.25)
P value	.81	.52	.86
Time to hospital discharge			
Hazard ratio (95% CI)	0.92 (0.75-1.12)	0.86 (0.72-1.03)	0.86 (0.69-1.07)
P value	.40	.10	.16

Abbreviation: CI, confidence interval.

**Table 4.** Propensity-Adjusted Logistic Regression Model for the Impact of Adjuvant Corticosteroids on High Hospital Charges  $\geq$ \$250 000

	Age Category, y		
	<1	1-5	>5
Odds ratio (95% CI)	1.19 (0.72-1.97)	1.62 (0.76-3.45)	1.22 (0.43-3.47)
P value	.48	.20	.69

Abbreviation: CI, confidence interval.

most of the studies were conducted at a time or place in which Hib accounted for most cases of meningitis, making it difficult to generalize the results. Our study included a large number of patients with bacterial meningitis cared for at tertiary care children's hospitals located in the United States.

In a randomized controlled trial published after the Cochrane review, Pelto et al<sup>11</sup> found adjuvant corticosteroids had no impact on overall mortality in 654 children with bacterial meningitis in Latin America. *Haemophilus influenzae* type b was the most common cause of meningitis, accounting for just over one-third of all cases of bacterial meningitis. The mortality rates for Hib meningitis (14.5%) and pneumococcal meningitis (22.7%) reported by Pelto et al<sup>11</sup> are higher than what have been reported in studies performed in the United States and other high-income countries.<sup>10,27</sup> Therefore, high prevalence of Hib and high-case fatality rates make it difficult to generalize these results to the United States where Hib is no longer prevalent and mortality is substantially lower.

In a more recent randomized trial of adults and adolescents with bacterial meningitis in Vietnam,<sup>7</sup> adjuvant corticosteroids were found to decrease

mortality in those patients with culture-confirmed bacterial meningitis, but had no significant effect on those with probable meningitis. In a subgroup analysis of meningitis caused by *S pneumoniae*, the results remained significant; however, only 55 patients had this diagnosis. The results were not stratified by age; therefore, it is unclear how many adolescents were included and what effect corticosteroid therapy had on this subset of patients when the median age of the study patients was 42 years.<sup>7</sup>

Our results did not change when we analyzed mortality by organism rather than age. The Cochrane review did not consider organism-specific mortality solely in children.<sup>10</sup> The review combined studies performed in adults and children and found a significant reduction in death from pneumococcal meningitis. However, the results may be driven to significance by the large effect adjuvant corticosteroids have on adults with pneumococcal meningitis, where the mortality rate without corticosteroids was 34% and with corticosteroids was 13.7%.<sup>6</sup> The largest pediatric study included in the Cochrane review's analysis of pneumococcal meningitis was conducted by Molyneux et al<sup>28</sup> in Malawi and showed no benefit

in mortality in children with pneumococcal meningitis. The study performed in Latin America dichotomized the data as Hib vs non-Hib meningitis, and no difference was found in mortality for either group.<sup>11</sup>

In contrast with the results from the Cochrane review, in an observational study, McIntyre et al<sup>9</sup> found that adjuvant corticosteroid use was associated with a lower odds of death in 120 children with meningitis due to *S pneumoniae* (odds ratio, 0.16; 95% CI, 0.025-1.00). The effect was also pronounced when a combined outcome variable that included death or severe morbidity was used (odds ratio, 0.21; 95% CI, 0.05-0.77). McIntyre et al<sup>9</sup> reported that 3 of 15 deaths (20%) in their study occurred in the first 24 hours of hospitalization. However, the distribution of deaths in their study beyond that point in time is not clear. The authors did not consider the timing of death in their analysis, which may account for differences in outcomes in our study and their study. For example, if most deaths occurred early in the course of hospitalization, the impact could be attributable to corticosteroid therapy. However, if the deaths occurred weeks or months later, the relationship of death to corticosteroids is less clear. In our analysis, 6 of 21 deaths (29%) attributed to pneumococcal meningitis occurred during the first 24 hours of hospitalization, similar to McIntyre et al<sup>9</sup>; however, 15 deaths (71%) in our study occurred during the first week of hospitalization. This demonstrates that the majority of deaths in children with pneumococcal meningitis in our study are not due to complications associated with long hospitalizations, which are most likely independent of corticosteroid receipt.

Our study results of no difference in mortality in children who received or did not receive corticosteroid therapy may differ from results of studies of adults for several reasons. First, adults may have different predisposing factors for meningitis or a different inflammatory response, either of which may alter the course of disease com-

pared with children. Second, the case fatality rate in pneumococcal meningitis in children is lower in comparison with the case fatality rate in adults with pneumococcal meningitis (4.2% vs 34%, respectively).<sup>6</sup> Our study could have been underpowered to determine a difference in mortality when case fatality rates are low in children with bacterial meningitis.

There was also no difference in the time to hospital discharge between children who received and did not receive corticosteroid therapy. Time to hospital discharge has not previously been studied as an outcome in children administered adjuvant corticosteroid therapy for bacterial meningitis. In an observational study on corticosteroids and pediatric sepsis, Markovitz et al<sup>29</sup> found that non-neonatal children who received corticosteroid therapy had a longer length of hospitalization compared with those who did not receive corticosteroid therapy. This variable is important because longer hospitalizations increase the risk of hospital-acquired complications.

Our study has several limitations. First, discharge diagnosis coding may be unreliable for specific diseases or pathogens. However, the mortality rates for children with bacterial meningitis in our study are similar to those published in studies performed in developed countries,<sup>9,10</sup> supporting the likely accuracy of our data. We also analyzed a subset of children identified with pneumococcal or meningococcal meningitis by ICD-9 discharge diagnosis codes in an attempt to reduce the error associated with misclassification, because unspecified categories may be more likely to include children without bacterial meningitis. Errors in discharge diagnosis coding could still have biased our findings toward the null hypothesis and the possibility remains of finding no benefit of adjuvant corticosteroid therapy when a benefit actually exists (type II error). However, the overall mortality rate in children with bacterial meningitis is substantially lower than mortality in adults. Therefore, any absolute reduction in mortal-

ity attributable to adjuvant corticosteroid therapy is likely to be minimal.

Second, there may be measured and unmeasured residual confounding by indication for adjuvant corticosteroid therapy related to illness severity. We included variables associated with severity of illness such as receipt of anticonvulsant therapy and vasoactive infusions in our propensity score. In addition, we found no difference in high hospital charges between those patients who received and did not receive corticosteroid therapy, suggesting that one group did not receive more intensive care. However, specific clinical factors potentially associated with increased illness severity such as the presence of cranial nerve palsy and hypothermia could not be assessed using administrative data. We also attempted to address the potential for miscoding corticosteroid receipt by restricting the analysis to children who had CSF cultures performed at participating hospitals, thereby excluding children transferred who may have received corticosteroid therapy at an outside facility. Misclassifying corticosteroid receipt or the timing of corticosteroid receipt may have also biased our results toward finding no difference.

Third, although the results of our subanalyses did not show a significant benefit of adjuvant corticosteroid therapy, the numbers of patients included in the various subgroups were relatively small, making it likely that our study was underpowered to detect small but significant differences in these subgroups. Therefore, we cannot exclude the possibility of the benefit of adjuvant corticosteroid therapy for certain subpopulations of patients with bacterial meningitis.

Fourth, we could not ascertain the dose or timing of corticosteroid administration. The potential benefit of adjuvant corticosteroid therapy would be less with inappropriate administration (eg, suboptimal dosing, administration after the first dose of antibiotics), a limitation that would bias our results toward the null hypothesis.

Finally, our study cannot address the possible benefits of adjuvant cortico-

steroid therapy on hearing loss or neurological morbidity. Adjuvant corticosteroid therapy may improve the long-term quality of life in some children with bacterial meningitis.

In conclusion, this multicenter observational study found that adjuvant corticosteroid therapy was not associated with survival or time to hospital discharge in children with bacterial meningitis. However, adjuvant corticosteroid use in the treatment of bacterial meningitis appears to be increasing. A randomized trial is warranted to explore the possible benefit of adju-

vant corticosteroid therapy on both morbidity and mortality in children with bacterial meningitis before such corticosteroid use becomes routine.

**Author Contributions:** Dr Shah had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis.

**Study concept and design:** Ten Have, Shah.

**Acquisition of data:** Mohamad, Shah.

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**Drafting of the manuscript:** Mongelluzzo, Shah.

**Critical revision of the manuscript for important intellectual content:** Mongelluzzo, Mohamad, Ten Have, Shah.

**Statistical analysis:** Mongelluzzo, Mohamad, Ten Have, Shah.

**Obtained funding:** Mongelluzzo, Shah.

**Administrative, technical, or material support:** Shah.  
**Study supervision:** Mongelluzzo, Shah.

**Financial Disclosures:** None reported.

**Funding/Support:** Dr Shah was supported by grant KL1RR024132 from the National Center for Research Resources. Ms Mongelluzzo was supported by the Doris Duke Medical Student Clinical Research Fellowship. This project was also supported in part by grant U18HS016946 from the Agency for Healthcare Research and Quality.

**Role of the Sponsors:** The funding organizations did not have any role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

**Disclaimer:** The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources, the Agency for Healthcare Research and Quality, or the National Institutes of Health.

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