

Community-Acquired Bacterial Meningitis in Adults: Categorization of Causes and Timing of Death

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The relationship between cause and timing of death in 294 adults who had been hospitalized with community-acquired bacterial meningitis was investigated. For 74 patients with community-acquired bacterial meningitis who died during hospitalization, the underlying and immediate causes of death were identified according to the criteria of the World Health Organization and National Center for Health Statistics. Patients were classified into 3 groups: category I, in which meningitis was the underlying and immediate cause of death (59% of patients; median duration of survival, 5 days); category II, in which meningitis was the underlying but not immediate cause of death (18%; median duration of survival, 10 days); and category III, in which meningitis was neither the underlying nor immediate cause of death (23%; median duration of survival, 32 days). In a substantial proportion of adults hospitalized with community-acquired bacterial meningitis, meningitis was neither the immediate nor the underlying cause of death. A 14-day survival end point discriminated between deaths attributable to meningitis and those with another cause.

During the past several decades, mortality rates for adults with bacterial meningitis have not decreased, despite progress in antibiotic therapy [1–5]. This observation has prompted studies that have investigated meningitis pathophysiology [6, 7], adjunctive therapies to suppress inflammation [1, 4, 7–9], and identification of prognostic indicators for clinical outcome [10, 11]. However, the accuracy of reported mortality for bacterial meningitis may be hindered by the crude measurement of hospital mortality and by the assumption that all hospital deaths are attributable to the case of meningitis that prompted admission.

Incorrect determination of the cause of hospital death is common, with reports of errors identified in

32%–59% of death certificates [12, 13]. Given the reliance on mortality data from epidemiological studies, major conclusions about public health and future health care recommendations may be based on erroneous information [12–18]. Assumptions about inpatient deaths due to bacterial meningitis may be inaccurate as well [14]; better specification is needed with regard to the time interval after admission in which death is attributable to meningitis. Identification of such a time interval will facilitate the accuracy of mortality data and will improve understanding of the impact of new interventions in clinical trials.

By use of the core definitions of “cause of death” as described by the World Health Organization [19] and by the National Center for Health Statistics of the US Department of Health and Human Services [20, 21], we analyzed the causes of death in adults hospitalized with community-acquired bacterial meningitis. Our hypotheses were as follows: a substantial proportion of adults who die during hospitalization for community-acquired bacterial meningitis die after resolution of the meningitis and die of a cause unrelated to meningitis;

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and adults hospitalized for community-acquired bacterial meningitis whose death is attributable to the meningitis die sooner after admission than do those whose death is due to an independent cause. Our specific aim was to define an optimal survival end point time for adults admitted with community-acquired bacterial meningitis during which death can be most accurately attributed to meningitis.

METHODS

A review of medical records and microbiology laboratory results at 4 Connecticut hospitals for the period of January 1970 through December 1998 identified 294 adults (>16 years of age) who had community-acquired bacterial meningitis diagnosed. To meet the definition of community acquisition, patients must have had a lumbar puncture within 24 h of presentation to the emergency department. In addition to a clinical picture consistent with meningitis, all cases required microbiological proof by fulfilling ≥ 1 of the following criteria: positive results of culture of CSF specimens, positive results of bacterial antigen or Quellung test of CSF specimens, CSF pleocytosis of ≥ 10 leukocytes/mL with a positive blood culture result, or the presence of gram-negative diplococci on a Gram stain of CSF specimens. Cases for which *Mycobacterium* species, *Treponema pallidum*, or *Borrelia burgdorferi* were the causative agent were excluded, as were patients with intracranial devices. For patients who had >1 episode of bacterial meningitis during the study interval, only the first episode was included. Characteristics of the portion of this cohort from January 1970 through December 1995 were well described in a recent study, which created a prognostic model of risk stratification for adverse clinical outcome [11].

Of the 294 adults who met the aforementioned criteria, 77 died during their hospitalization. The medical records of these patients were reviewed from time of admission until death. Four clinical features were identified at presentation and were followed to determine whether there was clinical resolution of the meningitis: altered mental status (lethargy, disorientation, or coma), hypotension (systolic blood pressure of <90 mm Hg or a drop in systolic or diastolic blood pressure of ≥ 40 mm Hg), seizures, and fever (temperature, $\geq 38.1^\circ\text{C}$ [100.5°F]). Each clinical feature was characterized as follows: "normalized," if it returned to the patient's baseline for at least 24 h continuously at any point during the hospital admission; "improved," if it returned to baseline, but for <24 h; "no improvement," if it never returned to baseline; "unknown," if it was not adequately evaluated or was attributable to another etiology; and "not applicable," if it was not a presenting feature. Clinical resolution of meningitis was then evaluated; all 4 criteria had to be normalized (or not applicable) to fulfill the definition of clinical resolution.

Independently, microbiological demonstration of meningitis was assessed at presentation and throughout the hospitalization. Microbiological resolution of meningitis was defined only if subsequent microbiological studies revealed a normalization of the initial criterion for microbiologically documented meningitis. For example, if the microbiological demonstration of meningitis was a positive CSF culture result, then a subsequent negative CSF culture result was necessary to prove microbiological resolution.

Cause of death, defined by the World Health Organization as "all those diseases, morbid conditions or injuries which either resulted in or contributed to death and the circumstances of the accident or violence which produced any such injuries" [19], was investigated in each case. In accordance with the National Center for Health Statistics of the US Department of Health and Human Services [20, 21], meningitis was considered the underlying and immediate cause of death if 1 of the sequelae directly caused by meningitis (specifically, coma, septic shock, or intractable seizures) were "the final disease, injury, or complication directly causing death" [20]. Coma (state of unresponsiveness to all stimuli excepting deep pain) was an immediate cause of death from meningitis if altered mental status (as a clinical feature at presentation) did not normalize and if the comatose state was continuously present for ≥ 12 h before death or ≥ 1 h before death if the patient died within 12 h of initiation of effective therapy. Septic shock (infection-caused systemic inflammatory response syndrome with hypotension in conjunction with at least 2 of the following criteria: fever [temperature, $\geq 38.1^\circ\text{C}$ (100.5°F)]; respiratory rate, >20 breaths per minute; heart rate, >100 beats per minute; or a most-recent serum WBC count of >12,000 cells/mL or <4000 cells/mL) was an immediate cause of death due to meningitis if hypotension (as a clinical feature at presentation) did not normalize and if the state of septic shock was continuously present for ≥ 12 h before death or ≥ 1 h before death if the patient died within 12 h of initiation of effective therapy. Intractable seizures (continuous or repetitively occurring with impaired consciousness between seizures) was considered an immediate cause of death from meningitis if seizures (as a clinical feature at presentation) did not normalize and if the state of intractable seizures was continuously present for ≥ 12 h before death or ≥ 1 h before death if the patient died within 12 h of initiation of effective therapy.

Meningitis was defined as the underlying but not immediate cause of death if it initiated the train of morbid events that led directly to death but the final disease, injury, or complication directly that caused death was not a direct sequela of meningitis. Examples of specific causes of death that fulfilled this definition included a complication from a procedure warranted by the diagnostic workup or treatment course of meningitis (e.g., ventilator-associated pneumonia) or a complication of meningitis treatment. Without the meningitis, these immediate causes of

Table 1. Demographics, clinical features, laboratory results, and causative organism among hospitalized adult patients with bacterial meningitis.

Variable	Patients who		P
	Died (n = 77)	Survived (n = 217)	
Demographic characteristic			
Age, median years (range)	65 (20–89)	53 (16–100)	.0009
Sex			
Male	36 (47)	116 (54)	.312
Female	41 (53)	101 (46)	.312
Ethnicity			
White	57 (74)	168 (78)	.529
Black	18 (23)	37 (17)	.529
Hispanic	2 (3)	10 (5)	.529
Asian	0 (0)	1 (0.5)	.529
Duration of symptoms, median days (range)	2 (0–14)	2 (0–30)	.327
Clinical feature			
Altered mental status	69 (90)	167 (77)	.001
Hypotension ^a	27 (35)	41 (19)	.001
Seizures	14 (18)	15 (7)	.005
Fever ^b	60 (78)	188 (87)	.071
Headache ^c	26 (60)	132 (84)	.001
Focal neurological examination	15 (20)	31 (14)	.235
Comorbidity ^d	48 (62)	85 (39)	.001
Immunocompromised state ^e	22 (29)	41 (19)	.230
Laboratory finding, median (range) ^f			
Serum leukocyte count, cells/mL	12,200 (700–73,300)	14,500 (1200–89,200)	.0027
CSF leukocyte count, cells/mL	188 (0–184,000)	1234 (0–96,000)	.0001
CSF protein level, mg/dL	274 (9–1860)	239 (10–2008)	.9484
CSF glucose level, mg/dL	33 (0–390)	33 (0–299)	.9447
Positive blood culture result	69 (93)	156 (73)	.001
Positive CSF Gram stain result	47 (62)	141 (65)	.591
Positive CSF culture result	69 (90)	180 (83)	.163
Causative organism			
<i>Streptococcus pneumoniae</i> ^g	41 (53)	100 (46)	.28
<i>Neisseria meningitidis</i>	2 (3)	41 (19)	.001
<i>Staphylococcus aureus</i> ^h	9 (12)	17 (6)	.306
Other streptococci ⁱ	12 (16)	22 (10)	.199
<i>Listeria monocytogenes</i>	6 (8)	13 (6)	.581
<i>Haemophilus</i> species ^j	0 (0)	11 (5)	.044
Non- <i>Haemophilus</i> species gram-negative rod ^k	4 (5)	8 (4)	.566
Mixed culture ^l	1 (1)	1 (0.5)	.456
Other ^m	2 (3)	4 (2)	.654

NOTE. Data are no. (%) of patients, unless otherwise indicated.

^a Systolic blood pressure of <90 mm Hg or a decrease in systolic blood pressure of \geq 40-mm Hg.

^b Temperature, \geq 38.1°C (100.5°F).

^c %, Number of patients with headache/no. for whom presence or absence of headache was recorded.

^d Charlson comorbidity scale score, \geq 1.

^e HIV infection (1 patient died, 7 patients survived) or AIDS (3 died, active cancer (14 died, 29 survived), corticosteroid use (11 died, 15 survived), asplenia (4 died, 12 survived), transplantation (1 survived), immunoglobulin deficiency (1 survived), neutropenia (1 survived), and pregnancy (1 survived).

^f Results unknown for \leq 6% of patients.

^g Three penicillin-resistant *S. pneumoniae* isolates, with MICs of 2.0 μ g/mL, in 1 patient who died and 1 who survived, and 0.1 μ g/mL, in 1 patient who died.

^h Two methicillin-resistant *S. aureus* isolates, both in patients who survived.

ⁱ Group B streptococci (6 patients died, 5 patients survived), group A streptococci (2 died, 4 survived), group G streptococci (1 died, 3 survived), *Streptococcus sanguis* (4 survived), viridans streptococci (2 died, 2 survived), *Streptococcus intermedius* (1 died, 1 survived), α -streptococci (1 survived), *Streptococcus salivarius* (1 survived), *Streptococcus bovis* (1 survived).

^j *Haemophilus influenzae* (in 9 patients) and *Haemophilus parainfluenzae* (in 2).

^k *Escherichia coli* (3 patients died, 4 patients survived), *Pseudomonas aeruginosa* (1 died, 1 survived), *Klebsiella pneumoniae* (1 survived), *Acinetobacter anitratus* (1 survived), *Enterobacter aerogenes* (1 survived).

^l *S. aureus* and *Klebsiella pneumoniae* (1 patient died); *S. pneumoniae* and *P. aeruginosa* (1 survived).

^m *Enterococcus* species (1 patient died [vancomycin-resistant strain], 2 patients survived), *Clostridium perfringens* (1 died, 1 survived), *Bacteroides* species (1 survived).

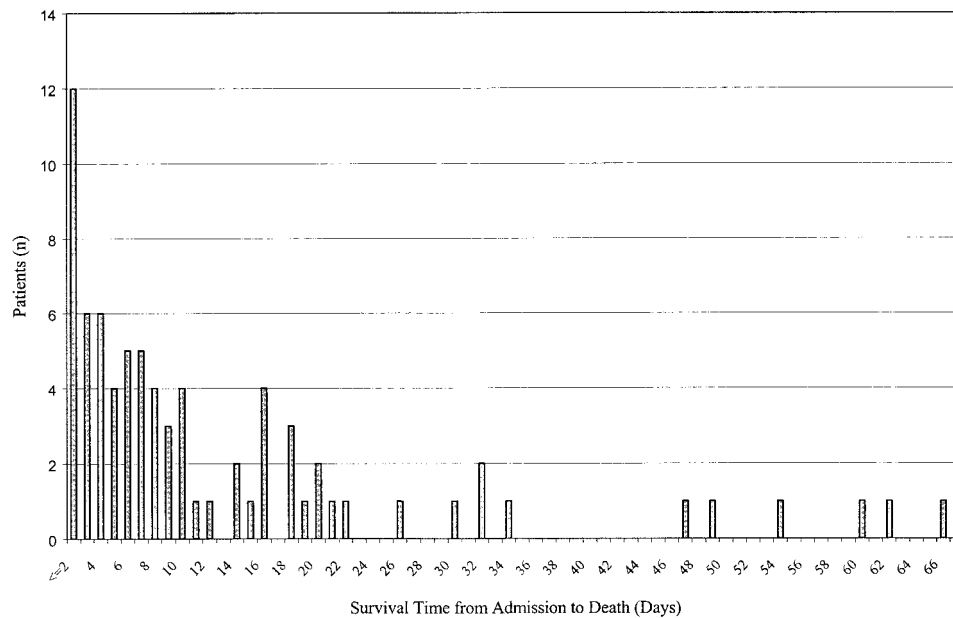


Figure 1. Survival time from admission to death of adults with community-acquired meningitis, expressed in calendar days in hospital, including date of admission. Therefore, date of admission at any time on calendar day 1 counted as 1 day of admission; if patient died any hour of calendar day 2, patient was categorized as death during ≤ 2 days of admission. No patients were admitted and died on same calendar day, so the shortest survival time recorded was ≤ 2 days.

death would not have occurred; however, the actual final disease, injury, or complication that caused death was not directly related to the presence of bacteria in the CSF. Therefore, meningitis was responsible for causing the death in an indirect manner.

Meningitis was considered neither the underlying nor immediate cause of death if a disease process unrelated to meningitis began >24 h after meningitis resolution and if it initiated the train of morbid events leading directly to death. In these instances, the cause of death could or would have occurred independent of the meningitis. Examples of this in our study included congestive heart failure, myocardial infarction, nosocomial bacteremia, aspiration, or other metabolic disease.

On the basis of the assessment of clinical and microbiological resolution, as well as cause of death, each episode was classified into 1 of 3 categories of cause of death. Category I included patients for whom meningitis was the underlying and immediate cause of death. Category II included patients for whom meningitis was the underlying but not immediate cause of death. Category III included patients for whom meningitis was neither the underlying nor the immediate cause of death. The proportion of patients classified in each category was determined. The median number of days between admission and death for all patients within each category of cause of death were compared. For statistical comparisons, differences in proportions were tested by use of the χ^2 test or Fisher's exact test. Contrasts of dimensional variables were tested using Student's *t* test and the Wilcoxon rank sum test.

RESULTS

Patient population. Among the 4 hospitals, 294 adults fulfilled the criteria of having community-acquired, microbiologically proven bacterial meningitis. Of 1115 medical records initially screened, 821 cases were excluded because of the following reasons: lumbar puncture was not done ($n = 162$), lumbar puncture was completed >24 h after presentation ($n = 189$), an incorrect diagnosis from the International Classification of Diseases, 9th revision, was applied ($n = 14$), the case definition was not fulfilled ($n = 356$), the medical record was incomplete ($n = 91$), or the patient's meningitis episode was not the first episode during the study period ($n = 9$). Of 294 patients with community-acquired bacterial meningitis, 77 patients (26%) died in the hospital.

Baseline features and microbial causes. Baseline demographics, clinical features, laboratory results, and microbial etiology are shown in table 1. Demographic characteristics of patients who survived ($n = 217$) were similar to those of the subgroup of patients who died ($n = 77$), although those who died had a greater median age (65 years vs. 53 years; $P < .001$). Fever, headache, and altered mental status were the most common clinical features overall, particularly in the subgroup of patients who died. Comorbid disease was present in approximately half of the entire cohort (47%), and it was more common in the subgroup of patients who died (62% vs. 39% in patients who survived; $P = .001$). Laboratory results were also

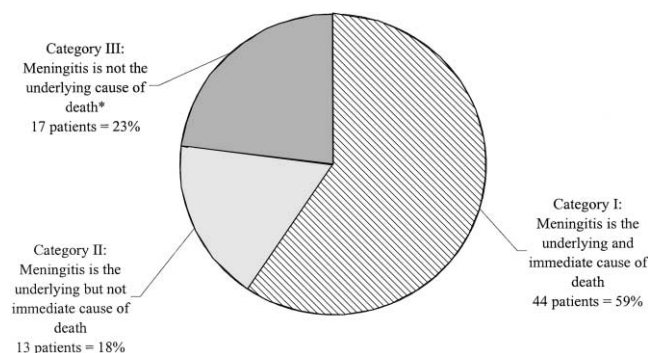


Figure 2. Categories of cause of death among hospitalized patients with meningitis. *Non-meningitis-related causes of death: aspiration pneumonia (in 2 patients), congestive heart failure (in 2), acute renal failure (in 2), fungal pneumonia (in 1), pulmonary hemorrhage (in 1), aspiration asphyxia (in 1), bacterial endocarditis (in 1), myocardial infarction (in 1), end-stage renal disease (in 1), recurrent urinary tract infection (in 1), septic shock from nosocomial bacteremia (in 1), thyroid cancer metastatic to lung (in 1), malignant hypercalcemia (in 1), and hyperkalemia (in 1).

similar between the 2 groups, with the exception of a lower median CSF leukocyte count and a higher proportion of positive blood culture results, which were found among patients who died. The most common causative bacterial pathogen was *Streptococcus pneumoniae*, which accounted for approximately half of the cases overall.

Survival time. For the 77 patients in the cohort who died, the duration between hospital admission and death is shown in figure 1. The number of survival days ranged from ≤ 2 to 66 (median, 8 days). Thirty-eight patients (49%) died within 7 days of admission, and 53 patients (69%) died within 14 days.

Categorization of cause of death. Three of the 77 patients who died could not be classified into a category of cause of death because of insufficient information in the medical record. As shown in figure 2, of the 74 patients whose cause of death was categorized, 44 (59%) had meningitis as the underlying and immediate cause of death (category I), 13 patients (18%) were classified into category II (i.e., meningitis was the underlying but not immediate cause of death), and 17 patients (23%) were classified into category III (i.e., meningitis was neither the underlying nor immediate cause of death).

Correlation between survival time and categorization of cause of death. Grouped into weekly intervals, the survival times of the patients within each category are shown in table 2. Thirty-three (75%) of 44 patients in category I died within 7 days of admission to the hospital, and 10 (77%) of 13 patients in category II died within 14 days of admission. Conversely, all 17 patients in category III died >14 days after admission. As outlined in table 3, there was a significant stepwise increase in median survival times from patients in category I (median survival time, 5 days; range, 2–30 days) to patients in category II

(median survival time, 10 days; range, 2–18 days) and category III (median survival time, 32 days; range, 16–66 days; $P = .0001$).

From these data, a 14-day time interval was identified to dichotomize survival for analysis: survival ≤ 14 days and survival >14 days. Patients in categories I and II were combined in a single group to represent patients in whom meningitis was at least the underlying cause of death (i.e., those in whom death was attributable to meningitis). This group was compared with patients in category III who died of a cause unrelated to meningitis. Table 4 illustrates the differences in 14-day survival between those patients who died of meningitis-related causes (i.e., meningitis was at least the underlying cause of death) versus those who died of other causes. Of those patients in whom meningitis was at least the underlying cause of death, 50 (88%) of 57 patients died within 14 days of hospital admission; all 17 patients for whom meningitis was not the underlying or immediate cause of death died after 14 days in the hospital ($P = .001$).

DISCUSSION

This study is the first to characterize and correlate the causes and timing of hospital death in a cohort of adults hospitalized for community-acquired bacterial meningitis. For a substantial proportion (23%) of patients with community-acquired bacterial meningitis who died in the hospital, meningitis was not the underlying or immediate cause of death. A survival end point of 14 days appeared to discriminate between deaths attributable to meningitis from those deaths that were attributable to another cause.

Table 2. Correlation between survival time and category of cause of death in hospitalized adult patients with bacterial meningitis.

Survival time, days	No. of patients in category		
	I ^a	II ^b	III ^c
0–7	33	3	0
8–14	7	7	0
15–21	3	3	6
22–28	0	0	2
29–35	1	0	3
36–42	0	0	0
43–49	0	0	2
50–56	0	0	1
57–63	0	0	2
64–70	0	0	1

^a Meningitis is underlying and immediate cause of death.

^b Meningitis is underlying but not immediate cause of death.

^c Meningitis is not underlying cause of death.

Table 3. Survival time, by categories of cause of death among hospitalized adult patients with bacterial meningitis.

Survival time, days	Category		
	I ^a	II ^b	III ^c
Median	5	10	32
Range	2–30	2–18	16–66

NOTE. For comparison of median survival times of 3 categories, $P = .0001$ (Wilcoxon test).

^a Meningitis is underlying and immediate cause of death.

^b Meningitis is underlying but not immediate cause of death.

^c Meningitis is not underlying cause of death.

The determination of cause of death is considered to be an inconsistent and poorly standardized decision process by clinicians [12–18]. To analyze deaths of adults hospitalized for community-acquired bacterial meningitis more accurately, strict definitions of meningitis-related causes of death were created in accordance with the criteria of the World Health Organization [19] and National Center for Health Statistics [20, 21].

In our study, we defined 3 clinical events to implicate meningitis as the immediate cause of death: coma, septic shock, or intractable seizures. Although multiple complications of bacterial meningitis may eventually result in death [1], these 3 complications were the most biologically and clinically plausible, on the basis of the known pathophysiology of the disease [6]. To be defined as a complication that “directly preceded death” [20, 21], it was required to be present for ≥ 12 h before death, unless death occurred within 12 h of initiation of therapy. Because any of these 3 conditions may be associated with disease processes other than meningitis, our study required that the patient exhibited the corresponding complication at clinical presentation. For those patients for whom meningitis was the underlying (but not immediate) cause of death, there was a wider variety of circumstances that led to death. Any constellation of events in which meningitis “initiated the train of morbid events leading directly to death” [19] implicated meningitis as the underlying cause of death. Although a complication from a procedure ($n = 2$) or a reaction to treatment ($n = 1$) specifically fulfilled the definition, patients in whom meningitis was the underlying cause of death were those in which the meningitis ultimately led to fatal events, such as respiratory failure, hepatic failure, or subacute bacterial endocarditis. These complications were the actual “final disease, injury, or complication directly causing death,” and, thus, they were considered to be the immediate cause of death.

If the event that led to death developed after the meningitis had resolved, it was logically assumed to be unrelated to meningitis. Therefore, our strict definitions for clinical and/or microbiological resolution of meningitis were important in iden-

tifying patients in whom the community-acquired meningitis was not the immediate or underlying cause of death.

As shown in figure 1, half of the patients in our cohort who died of community-acquired bacterial meningitis died within 1 week of hospitalization; two-thirds died within 2 weeks of admission. However, the range of survival before death was wide (2–66 days), and 24 (31%) of 77 deaths occurred after 14 days of hospitalization. This observation raised the possibility that many patients who died later in their hospital course may have died of an independent cause after resolution of the admitting meningitis. The demonstration in figure 2 that 23% of patients died of an unrelated cause that began after resolution of the meningitis emphasizes that meningitis should never be assumed to be the cause of death, despite the fact that it was the admitting clinical problem. Although death certificates were not reviewed as part of our study, one could reasonably expect that many physicians extrapolated cause of death from the primary admitting diagnosis and, therefore, a significant percentage of death certificates listed an incorrect cause of death.

The correlation between cause of death and survival time was analyzed in 2 ways. First, median survival times were compared among the 3 categories for cause of death (table 3). As shown in table 3, the median survival time was significantly shorter if meningitis was the immediate cause of death (category I) than it was if meningitis was only the underlying cause of death (category II) or was unrelated to the cause of death (category III; $P = .0001$). This observation has clinical and biological plausibility. Because meningitis is a rapidly progressing disease [3, 4, 8, 9], death would be expected to occur sooner [8, 22–24] when it is more directly related to the community-acquired meningitis.

Second, when survival time was dichotomized to ≤ 14 or >14 days (table 4), meningitis was at least the underlying cause of death in all patients who died within the 14-day time period; all 17 patients for whom meningitis was not the cause of death died after 14 days of hospitalization.

Table 4. End point survival time among hospitalized adult patients with bacterial meningitis.

End point survival time, days	Categories	
	I and II ^a	III ^b
≤ 14	50	0
>14	7	17

NOTE. For proportion of deaths within 14 days in categories I and II combined compared with category III, $P = .001$.

^a Meningitis is underlying cause of death.

^b Meningitis is not underlying cause of death.

Despite the methodological advantages and strict definitions used in our study, there were limitations. First, retrospective data collection raised the risk of missing information and detection bias. However, our explicit definitions of cause of death and meningitis resolution minimized this bias, and all causes of death were confirmed by 2 investigators. Second, not all deaths in which meningitis was the immediate or underlying cause were captured within the 14-day time period. However, the 14-day survival time discriminated well, combining both sensitivity (i.e., 50/57 = 88%) and specificity (17/17 = 100%) in determining whether death was attributable to the admitting meningitis (i.e., meningitis was the immediate or underlying cause of death).

These data suggest that future studies of community-acquired bacterial meningitis use a 14-day survival end point to more accurately discriminate deaths attributed to meningitis from those that have another cause. This end point will facilitate greater accuracy of epidemiological statistics and will assist investigations of the impact of new therapeutic interventions.

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