Long-term Sequelae of Childhood Bacterial Meningitis

An Underappreciated Problem

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Background: Numerous sequelae have been noted in survivors of bacterial meningitis; however, few studies document sequelae for several years following a childhood episode of bacterial meningitis. In addition, studies generally focus on the more commonly found sequelae. To review the known information and highlight this gap, this article presents a comprehensive literature review of the long-term (>5 years of follow-up) sequelae of childhood bacterial meningitis.  

Methods: A systematic literature search was conducted between December 2009 and February 2010. English-language articles published between January 1970 and January 2010 were selected for screening. Articles were included if the subjects were between the ages of 1 month and <18 years at the time of diagnoses of meningitis.  

Results: A total of 1433 children who were survivors of childhood bacterial meningitis were evaluated for sequelae after the time of discharge. Of these children, 705 (49.2%) were reported to have 1 or more long-term sequelae. A majority of reported sequelae were behavioral and/or intellectual disorders (n = 455, 45.0%). Hearing changes accounted for 6.7% (n = 68) of sequelae and gross neurologic deficits accounted for 14.3% (n = 145).  

Discussion: A majority of childhood bacterial meningitis survivors with long-term sequelae that are documented in the literature have academic and behavioral limitations. While neurologic deficits may resolve over time, subtle behavioral deficits may not be appreciated initially and may continue to affect survivors for many years. Further studies are needed to quantify the true societal and economic burden of long-term sequelae as well as fully understand the breadth of types of sequelae that survivors experience.  

Key Words: bacterial meningitis, long-term sequelae, neurologic deficits, cognitive delay  

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In spite of the availability of preventive vaccines and effective antibiotics, bacterial meningitis remains a significant cause of morbidity and mortality in the United States. In the United States, the overall annual incidence of meningitis is between 2 and 10 cases per 100,000.1 Due to the successful implementation of preventive vaccines for bacterial meningitis, Haemophilus influenzae type b and Streptococcus pneumoniae (S. pneumoniae), Neisseria meningitidis is now the leading cause of bacterial meningitis in the United States, particularly in infants less than 1 year of age.2,3  

Surveillance in the United States from 1998 to 2007 showed a total of 2262 cases of meningococcal disease, with 50.2% of those cases being meningitis.4 Despite the availability of appropriate treatment, the case fatality rate from meningococcal meningitis during that time period in United States was 9.0%.  

Numerous sequelae have been noted in survivors of childhood bacterial meningitis including seizure disorders, focal neurologic deficits, hearing/vision loss, and impaired cognitive functioning.1 Sequelae vary based primarily on the etiologic agent, but overall, approximately 25% of survivors in the United States have moderate or severe sequelae.5–7 Several studies have described and quantified these sequelae, supplementing patient experiences with detailed neurologic exams, and studies.6,8–10 Studies have also begun to elucidate the economic costs (both on individual and societal levels) associated with bacterial meningitis.11 These data will help to further inform recommendations for conjugate vaccines against common etiologic agents of meningitis.  

In general, most studies have followed patients for no more than 5 years following their initial infection. Studies documenting the long-term sequelae noted 10, 20, or 30 years following a childhood episode of bacterial meningitis are limited. In addition, studies generally focus on the more commonly found sequelae such as those listed above, and do not elucidate the breadth of sequelae including joint problems or inability to fulfill professional responsibilities. To review the known information and highlight this gap, this article presents a comprehensive literature review of the long-term (at least 5 years of follow-up) sequelae of childhood bacterial meningitis.  

MATERIALS AND METHODS  

A systematic literature search was conducted between December 2009 and February 2010 using PubMed/Medline, Embase, and the Cochrane Library. Search terms were based on the key words and mesh headings for “bacterial meningitis” and at least one of the following key words and/or mesh headings: neurologic manifestations, hearing change, vision change, joint disease, learning disorder, language development disorder, and mental retardation (MR). English-language articles published between January 1970 and January 2010 were selected for screening. Additional articles were identified from the bibliographies of all articles retrieved.  

Citations were de-duplicated, and then reviewed by 2 screeners. Articles were included if the subjects were between the ages of 1 month and less than 18 years at the time of diagnoses of meningitis and included prospective and retrospective studies, as well as case reports. Review articles were excluded. Articles that also included neonates and/or adults were included only if they specifically referenced children between 1 month and less than 18 years of age and data pertaining to these children could be extracted from the study population; in these cases, only these subjects were included in our analysis. Articles that reported a full recovery at the time of follow-up were excluded from the study. For the purposes of this study, “sequelae” was defined as a
complication that resulted from childhood bacterial meningitis that was present at or developed after the time of discharge and persisted during the follow-up period. Articles that did not specifically include a follow-up encounter after the patient had been discharged from the hospital were excluded from the study.

Sequelae included hearing loss, vision loss, cognitive delay (including mental retardation [MR] and learning disabilities), speech and language deficits, behavioral problems, and motor delay and impairment. Deaths were reported if they occurred after the patient was discharged from the initial hospital admission but during the follow-up period, and were directly associated with sequelae from meningitis. Motor deficits were defined as spasticity, paresis, or paralysis of 1 or more limbs. Seizures were defined as a seizure disorder of any type that was present after hospitalization. Deafness was defined as a hearing loss of at least 30 decibels (dB) in 1 or both ears. Severe/profound deafness was specified if identified by the authors. For patients with multiple sequelae, each sequela was identified.

Articles were then reviewed for the length of time after diagnosis that subjects were followed/assessed. All articles that had at least 1 subject that was ≥5 years after initial diagnosis were included in this review.

RESULTS

A total of 1648 citations were initially identified (Fig. 1). All citations were screened, and 1071 were excluded as they did not meet the inclusion criteria. In these cases, the article’s title did not refer to consequences/sequelae of meningitis, or did not reference children in the appropriate age group. Among these, 12 meta-analyses were examined, and the cited references from these articles were included in the screening process. Of the remaining articles, 445 were excluded as they did not specify a follow-up period, did not specifically identify children aged 1 month to less than 18 years of age, or did not identify meningitis sequelae. About 31 articles were not available for review, primarily because they were from obscure older international journals, a majority of which are from publishers that no longer exist. About 72 articles identified sequelae attributed to bacterial meningitis at a time following discharge, of which 24 specified a follow-up period of equal to or greater than 5 years and were included in this study. Table, Supplemental Digital Content 1, http://links.lww.com/INF/A556 presents the sequelae identified in each publication at the time of follow-up evaluation. A majority of the articles (83.3%) were published in North America (n = 7), Europe (n = 9), and Australia (n = 4). The remaining 16.7% of articles were published in Africa (n = 2) and Asia (n = 2). Eight articles (33.3%) described learning disability, mental delay, and/or MR. Five articles (20.8%) described neurologic deficits. Six articles described multiple neurocognitive sequelae. Others described sequelae including hearing deficits (16%) and joint impairment (4.1%).

The time from discharge to the maximum follow-up period of a survivor for sequelae, as reported in each publication, had considerable variation. Two publications reported a maximum follow-up period of 5 years, whereas 10 publications reported a maximum follow-up period of 10 years. Five publications reported a maximum 15-year follow-up; 3 publications reported a maximum 20-years follow-up, and 2 publications reported a follow-up period greater than 20 years (Fig. 2).
A total of 1433 survivors of childhood bacterial meningitis (excluding those that appeared to be reported in more than 1 publication12–14) were evaluated for sequelae after the time of discharge. Of these, 705 (49.2%) children were reported to have 1 or more long-term sequelae, of which more than one-third of the cases were attributed to H. influenzae (n = 260; 36.9%). A total of 82 (11.6%) children with sequelae had tuberculous meningitis, 27 (3.8%) had S. pneumoniae, and 16 (2.7%) had N. meningitidis. In the majority of cases (n = 314; 44.5%) that reported long-term sequelae of childhood bacterial meningitis, the etiology of bacterial meningitis was not specified.

Of the 705 children with sequelae, there were 3 deaths (0.4%) which were directly attributed to sequelae of meningitis due to cerebral infarction (n = 2) and “brain destruction” (n = 1).15,16 There were a total of 1012 reported sequelae, of which a majority were behavioral or intellectual deficits (n = 792, 78.3%). Specific diagnoses and conditions include low intelligence quotient (IQ)/cognitive impairment (n = 455, 45.0%), attention deficit hyperactivity disorder (n = 24, 2.4%), and behavioral deficits (n = 77, 7.6%). Hearing deficits accounted for 6.7% (n = 68) of sequelae and gross neurologic deficits accounted for 14.3% (n = 145). There were 3 accounts of vision deficits and 1 complaint of limb pain. Table 1 describes specific sequelae, as it relates to each category. Sequelae such as cortical atrophy, headaches, sensory deficits, nystagmus, optic atrophy, optic arachnoiditis, hemianopsia, arthritis, and scarring did not appear in articles that followed the time of hospital discharge, which describe a much higher prevalence of neurologic and hearing deficits.7,9,17,18 For example, the literature review by Ramakrishnan et al (2009) looking at sequelae from bacterial meningitis among African children found that a median of 25% of children had 1 or more neuropsychological sequelae.9 In the majority of reviews, the follow-up period was not defined.7,9,17

By defining “long-term” as a follow-up period of 5 or more years, our review showed that the majority of survivors with sequelae that are documented in the literature described academic and behavioral limitations. Minor neurologic deficits have been shown often to resolve after discharge. In a large prospective study, Feigin et al (1992) found that nearly one-third (32.8%) of all children with bacterial meningitis had neurologic deficits at the time of discharge; however, 5 years later, only 11.1% had documented ongoing abnormalities.19 In contrast, subtle neurologic deficits, such as impaired school performance, behavioral problems, and attention deficit disorder, may not be appreciated initially and may continue to affect survivors for many years.

Because of the inclusion/exclusion criteria used in our analysis, several important studies related to the long-term sequelae of bacterial meningitis are not included in this review.20–23 Many of these authors’ findings reflect similar results as what our review showed; for example, Sell et al note that 2 survivors had a

| TABLE 1. Burden of Long-term Sequelae From Childhood Bacterial Meningitis |
|-----------------------------|-----------------------------|
| Long-term Sequelae          | No. Sequelae (n = 1012) (%) |
| Death                       | 3 (0.3)                     |
| Intellectual/behavioral deficits | 792 (78.3)                 |
| Low IQ/cognitive impairment | 455 (45.0)                  |
| Academic limitations        | 206 (19.9)                  |
| ADHD                        | 24 (2.4)                    |
| Behavioral deficits*        | 77 (7.6)                    |
| Mental retardation          | 30 (3.0)                    |
| Hearing deficits            | 68 (6.7)                    |
| SNHL                        | 14 (1.4)                    |
| Conductive loss             | 3 (0.3)                     |
| Not specified               | 51 (50.0)                   |
| Vision deficits             | 3 (0.3)                     |
| Cortical blindness          | 1 (0.1)                     |
| Not specified               | 2 (0.1)                     |
| Neurologic deficits         | 145 (14.3)                  |
| Seizures/epilepsy           | 18 (1.8)                    |
| Motor deficits†             | 30 (3.0)                    |
| Cerebral palsy              | 5 (0.5)                     |
| Not specified               | 92 (9.1)                    |
| Joint impairment            | 1 (0.1)                     |
| Limb pain                   | 1 (0.1)                     |

*Behavioral deficits include emotional disturbances.
†Motor deficits include motor weakness, vestibular dysfunction, balance deficits, ataxia, spastic quadriplegia, choreoathetosis, tremor, and/or hemiatrophia.

ADHD indicates attention deficit hyperactivity disorder; SNHL, sensorineural hearing loss; IQ, intelligence quotient.


**DISCUSSION**

Despite appropriate antibiotic therapy and the availability of vaccines, bacterial meningitis in children is associated with a high risk of long-term sequelae. Our review showed approximately half (49.1%; n = 705/1433) of long-term survivors (specified as having a follow-up time at least 5 years) of childhood bacterial meningitis experience sequelae, of which a majority (78%) were intellectual and/or behavioral deficits. Just over 20% of survivors suffered long-term from hearing changes or neurologic deficits.

This observation differs from other comprehensive literature reviews, which define “long-term” as occurring any time following the time of hospital discharge, which describe a much higher prevalence of neurologic and hearing deficits.7,9,17,18 For example, the literature review by Ramakrishnan et al (2009) looking at sequelae from bacterial meningitis among African children found that a median of 25% of children had 1 or more neuropsychological sequelae.9 In the majority of reviews, the follow-up period was not defined.7,9,17

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Because of the inclusion/exclusion criteria used in our analysis, several important studies related to the long-term sequelae of bacterial meningitis are not included in this review.20–23 Many of these authors’ findings reflect similar results as what our review showed; for example, Sell et al note that 2 survivors had a
15-point IQ deficit compared with healthy sibling controls, while Sumaya et al showed that a group of 21 long-term survivors showed poor ratings in school and in employment.\(^\text{22,23}\)

The reporting of long-term sequelae of bacterial meningitis varies widely; some authors focused on 1 specific type or category of sequelae, whereas other authors reported all sequelae. Most articles did not include a control/comparison group, which is particularly important for understanding the amount of cognitive and neuropsychological impairment that can be attributed to childhood bacterial meningitis. Some sequelae, such as joint problems, are investigated and reported with low frequency, so the true burden of those sequelae is likely underestimated. Some articles only reported on a cohort of patients who had a particular sequela, therefore not providing information on the incidence of that outcome. Information for some \((n = 7)\) of the patients included in this analysis came from case reports, which are clearly not designed to capture the breadth of information that is available from prospective studies with larger cohorts. Finally, diagnostic methods vary widely between publications. Classification of diagnoses, for example “severe hearing loss,” varies widely between authors, making it difficult to quantify the magnitude of each sequela.

Despite these limitations, this comprehensive review clearly demonstrates that childhood bacterial meningitis is associated with substantial long-term sequelae in survivors. As decisions are made about recommendations for use of conjugate vaccines against common etiologic agents of meningitis, the full impact of long-term sequelae should be an important consideration. Further studies from a variety of geographic and sociodemographic settings are needed to quantify the true societal and economic burden of long-term sequelae as well as to fully understand the breadth of types of sequelae that survivors experience.

REFERENCES