Title: Clinical features, acute complications, and outcome of Salmonella meningitis in 24 children under one year of age in Taiwan

Authors:

Hung-Ming Wu (whmhwy@gmail.com)
Wan-Yu Huang (juliahuang01@gmail.com)
Meng-Luen Lee (lee.ml58@gmail.com)
Albert D Yang (yangad45@yahoo.com.tw)
Ko-Ping Chaou (chaoukp23@yahoo.com.tw)
Lin-Yu Hsieh (hsiehly89@yahoo.com.tw)

Version: 3 Date: 1 December 2010

Author’s response to reviews: see over
Nov 30th, 2010

Dear Editor,

We would like to express our deep thanks for your responsive letter with valuable comments. We sincerely appreciate the reviewers’ suggestions and comments on our manuscript. Please find enclosed point-by-point responses to the reviewers and the revised manuscript, in which all changes were highlighted with blue color. The consents we obtained have been clarified in the revised text. We hope that the revised manuscript will be acceptable for publication in BMC Infectious Diseases. We look forward to hearing from you.

Best Regards,

Hung-Ming Wu, MD, Ph.D.
Response to Reviewers

Reviewer #1 (Comments to the Author):

Reviewers report:
The article by Wu et al describes a retrospective cohort of 24 children with Salmonella meningitis admitted from 1982-1994 with follow-up data. The data are interesting but the manuscript can be substantially shortened (especially the discussion).

Response:
We will do our best to shorten the discussion by making each sentence more concise.

Comments:
1-The authors claim to perform a prospective analysis in a retrospectively collected cohort. The follow-up examination can be better characterised as a cross-sectional analysis in survivors as the follow-up was performed at different time-points after the meningitis episodes.

Response:
We appreciate your valuable comments. It would be better if more follow-ups were performed at different time points after the meningitis episodes. This would allow us to describe absolute risks, not only relative risks, for the outcome of Salmonella meningitis by cross-section. Actually, our cases were followed up at school age. We believe your comments will be very helpful for future study.

2-It is not mentioned if any patients were HIV positive or if there were other risk factors present for severe infections.

Response:
Thank you very much for mentioning this. The first local HIV-1 infection in Taiwan was reported on February 1986. It was a very rare incidence of an HIV-1-infected (+) female and vertical HIV-1 transmission before 1996 (Centers for Disease Control, ROC (Taiwan), HIV/AIDS, 2006). Infants and neonates with Salmonella meningitis were not routinely tested for HIV during the period of 1982-1994. Their birth and development histories before Salmonella infection were normal, and their Salmonella meningitis was spontaneous, not nosocomial. It is believed that there were no specific risk factors such as HIV-1 in our cases.
3-It should be described whether initial antibiotic treatment covered Salmonella in all patients.

Response:
Thank you very much for your suggestion. During the period of 1982-1994, 24 cases of Salmonella meningitis were admitted to our hospital for first aid. Blood and CSF cultures and Gram stains were performed routinely for our cases. This sentence, “Initial antibiotics that covered Salmonella species were used for the twenty-four patients, based on the results of gram stains and cultures of blood and CSF:” was added (Page 9, Line 19-20).

4-Was CT available during the whole study period at the study site? In 1982 CT might not have been widely available and MRI certainly wasn’t. Therefore the rate of intracerebral complications might be underestimated. This should be mentioned in the discussion. The nr of patients in which brain sonography, CT-scan and ventricular tap were performed should be mentioned. The complications should be given as nr/nr evaluated (%) unless all patients received adequate brain imaging.

Response:
Thank you very much for your kindly suggestions. CT scan has been available since 1980 in our hospital. The exact number of cases in which brain CT imaging (N =18), sonography (N = 22), and ventricular tap (N = 12) were performed is shown in the results section (Page 10, Lines 10-11) as suggested. In addition, “underestimated complication rate” was added to the discussion.

5-The cohort is quite old and therefore treatment of these patients might not be considered adequate according to current standards. The authors should discuss potential changes in current population and antimicrobial susceptibility compared to their cohort (e.g. dexamethasone treatment, improved critical care facilities, new antibiotics). The authors should discuss current optimal treatment for Salmonella meningitis in children.

Response:
These suggestions are very useful. A brief discussion was written (Pages 15-16, Lines 17-20, and 1-11). Please see below.

“Treatment of Salmonella meningitis has not been well defined. Conventional antimicrobial agents, including chloramphenicol, ampicillin, and cotrimoxazole, had a low cure rate (~ 40%) and a highly associated mortality (~ 45%) [23]. Third-generation cephalosporins and fluoroquinolones had a high cure rate (> 80%) and a lower associated mortality (< 10%) [10, 24-26]. Thus, those two antibiotics would be regarded as the optimal antimicrobial regimens in the treatment of Salmonella meningitis [26]. All our patients were treated with susceptible antibiotics, and most received third-generation cephalosporins, combined with chloramphenicol or ampicillin. Similar to the
previous report [10], the mortality rate in our cases declined to about 10%, but the morbidities remained high, up to 75%. The results suggest that susceptible antibiotics for treatment of *Salmonella* meningitis in children are unsatisfactory. Adjunctive dexamethasone, therefore, may be recommended to attenuate the effects of the acute innate inflammatory response to bacterial invasion within the CNS [27,28], although the benefits of steroids in meningitis seemed controversial in developing countries [29]. In addition, the patient should be monitored in the intensive care unit for any morbidity, such as seizure, in order to detect its potential complication.”

6-The outcome classification on the modified 5 point scale is not very useful; it mixes functional outcome with neurological investigation or imaging. Hydrocephalus without complaints for instance is considered a 'mild adverse outcome' while the patient is perfectly fine. It would be better to use the Glasgow Outcome Scale or Modified Ranking Scale.

**Response**

We appreciate your valuable suggestions. The Glasgow Outcome Scale is the most widely used to assess the outcome of traumatic brain injury. It is believed that the Glasgow Outcome Scale could also be a good tool to assess the outcome of children with CNS infection. However, it may have some specific limitations because there are no guidelines for dealing with commonly encountered problems, such as epilepsy and extracranial injury (Anderson et al., 1993; Boake, 1996). Bacterial meningitis (e.g. *Haemophilus* influenza and *Salmonella* meningitis) usually results in complicated sequelae. The seizure disorders and potential sequelae are considered to be taken into account on the scale. Therefore, we tried to use a previous scale that measured the outcome of childhood HI meningitis (McIntyre et al., (1993) to evaluate the outcome of *Salmonella* meningitis.

7-In the tables data should be given as nr/nr evaluated (%) unless all data were available for all patients which is hard to imagine in a 28 year old retrospective cohort.

**Response:**

Thank you very much for mentioning this. Our study was approved by our hospital ethics committee in 1994. The 13-year (1982-1994) charts of the patients with *Salmonella* meningitis were revealed in 1994. Fortunately, their recordings of *Salmonella* events were fully preserved in our hospital.

8-The CSF values should be presented as medians with interquartile ranges.

**Response:**

We would like to thank you for your valuable suggestions. The CSF values in Table 2 were presented as medians with interquartile ranges.
9-The text in the results “Four children were found to have intracranial infections” should be changes to “Four children were found to have focal intracranial infections”

Response:
Thanks for your correction. The word “focal” has been added to this sentence (Page 10, Line 19).

10-Discussion: 2nd paragraph 3rd sentence is not correct English; it’s unclear what the authors want to say.

Response:
Thank you very much for your correction. The paragraph was re-written to discuss mortality, morbidity and current optimal treatment for Salmonella meningitis in children as you suggested (Pages 15-16, Lines 18-20, and 1-12). Please see the response to Comment 5.

11-The discussion about early and late seizures can be omitted. Seizures in this patient group are clearly related to the severity of brain damage and intracranial complications.

Response:
We agreed with your suggestion to omit this paragraph.

12-Table 3 does not add much, except for the first column stating the total nr of survivors with sequelae. This should be combined with the outcome data of table 1.

Response:
Thank you very much for your suggestion. Previous studies have shown that Salmonella meningitis has a wide spectrum of acute CNS complications including brain edema, intracranial pressure increase, hydrocephalus, subdural effusion, cerebrovascular lesion, intracranial focal infection, and seizure activity (Kavaliotis, Scand J Infect Dis 1994; Messer, J Paediatr Child Health 1997; Huang, Acta Paediatr 1997; Visudhiphan, Trans R Soc Trop Med Hyg 1998; Lee, J Paediatr Child Health 1999; Sirinavin, Pediatr Infect Dis J 2001; Sangaré, Bull Soc Pathol Exot 2007). The results of the present study were consistent with previous findnings. We also revealed that most of those complications often occur with other complications, leading to a much complicated clinical illness course and outcome (Table 3). We believe this information will provide more insight into the spectrum of complications of Salmonella meningitis for readers.
Coma is only mentioned in table 4, but not in table 1 or in the results. The definition of coma and other levels of decreased consciousness should be given. If available Glasgow coma scale scores would be preferable.

**Response:**

We would like to thank you for your valuable suggestion to give the definition of consciousness levels in this study. The Glasgow Coma Scale (GCS) is widely accepted as a measure of impaired consciousness, both in clinical practice and in research since 1974 (Teasdale, Lancet 1974; 2: 81-84). In its standard form, the scale is inapplicable to infants and children below the age of 5 years, and modified GCS for children was reported early in 1982 (Simpson and Reilly, Lancet 1982). In our hospital, the modified Grady coma scale has been routinely used to measure the level of consciousness, classing children on a scale of I to V. This score was added in Table 4 and in the method section (Page 6, Lines 9-13): “In this study, the modified Grady coma scale was used to measure the level of consciousness, classing children on a scale of I to V along a scale of lethargy or irritability (grade I), stupor (grade II), deep stupor (grade III), coma with abnormal posturing (grade IV), and coma without any response (grade V) [16].”
Reviewer #2 (Comments to the Author):

The authors report short and long-term outcome on 24 children with *Salmonella* meningitis in the first 12 months of life. I believe previous studies have involved smaller numbers of patients with less complete follow-up.

**Mandatory revisions:**

The title is appropriate, but should clarify the age group that was studied.

**Response:**

Thank you very much for your valuable suggestion. The article has been changed to “Clinical features, acute complications, and outcome of *Salmonella* meningitis in 24 children under one year of age in Taiwan”

Abstract

1. First sentence of methods – What do you mean by “primary patients”? The same term is used multiple places in the manuscript and I never could figure out what you meant.

**Response:**

Thank you very much for mentioning this. The term “primary patients” was sometimes used in literature, and may not make sense to readers. So, the word “primary” was omitted from our manuscript. Instead, we described our patients in the methods section (Page 9, Lines 4-5): “We collected one to three cases with *Salmonella* meningitis annually for a total of twenty-four patients (six neonates and eighteen infants) who had not received any treatment for the illness before coming to our hospital.”

2. In Results where complications are listed, you need to clarify that you mean intracranial abscess. Also, “abducens” is spelt incorrectly here and later in the body of the manuscript.

**Response:**

Thank you very much for your correction. The word “abscess” was changed to “intracranial abscess” in the abstract and in the results section (Page 10, Line 14). “abducent palsy” was changed to “abducens nerve palsy” in the abstract and the result section (Page 10, Line 19), (Page 12, Line 12), and Table 3.

3. Conclusion – A word is missing from the first sentence. In the second sentence, it is not clear what you mean by “a refining procedure”.

**Response:**

We appreciate your correction. The missing word “complications” has been added to the first sentence. The second sentence was changed to “Thus, early recognition of acute complications of *Salmonella* meningitis and a follow-up plan for early developmental assessment of survivors are vital.”
Background

4. In the first sentence, “central nervous system infections of childhood bacterial meningitis” does not make sense.

Response:
Thank you so much for the kindly correction. The words “central nervous system infections of” were omitted from this sentence (Page 5, Line 1): “Salmonella strains are an important pathogen in childhood bacterial meningitis in many developing countries.”

5. In the sentence “The Previous reports suggested that Salmonella meningitis was associated with a very high prevalence (50-90%) of morbidity presenting with variable complications, and a high mortality rate of up to 50-70 %.” the word “previous” should not be capitalized.

Response:
We appreciate your correction. The word “Previous” was de-capitalized (Page 5, Line 7).

Methods

6. Why did you not enroll patients infected after 1994? Follow-up was only until school age so one would think even those enrolled in 2000 could all have completed follow-up by the time the data was collected. What was the upper limit of age for children you considered to be eligible?

Response:
From 1982-1994, we collected one to three cases with Salmonella meningitis annually for a total of 26 patients. 24 of them received first aid and all medical care in our hospital, and the other two were referred to us after partial antibiotic treatment by local medical care. After 1994, only a few cases with Salmonella meningitis were collected in our hospital due to public health improvements in Taiwan, and they were referred by local medical care. Since the group of referred cases with Salmonella meningitis was small and treated with varied durations of antibiotics before admission, this group was excluded from our study. Salmonella meningitis almost always occurs in neonates and infants (≤ 1 year old). In this study, all cases were under the age of one year.

7. In methods where you talk about language development, you need to clarify that you are referring to SD from the mean.

Response:
Thank you very much. The variation from the mean of normal children is one SD for the language development test. These words were added to the sentence (Page 7, Lines 6-7): “Language ability was assessed with a language assessment test (one and a half standard deviations from the mean of normal children) as previously described”
8. You need to briefly explain the analysis that is presented in Tables 3 and 4.

Response:
Thank you very much for your suggestion. A small paragraph was added in the method section (Page 8, Lines 7-11). “Data is expressed as mean ± SD or median (range). Clinical features at the time of admission and acute complications of Salmonella meningitis were evaluated to find the relevant predictors associated with death, severe adverse outcome, and moderate adverse outcome using the 2-tailed Fisher’s exact test (SPSS for Windows, version 15, SPSS Inc, Chicago, IL). P value < 0.05 was considered significant.” A brief explanation of the analysis was presented in Table 4 and the discussion section (Page 15, Line 14).

9. Everything should be in the same order in Methods as in Results.

Response:
Thank you very much for mentioning this. We will carefully check that everything is in the same order in those sections.

Results
10. It would be unusual if all eligible patients came for follow-up years later. You need to say how many eligibles were not followed up and how many had incomplete testing.

Response:
Our hospital is a Christian hospital. We have a very good team of social workers to help people who are sick or who have health problems. In that period, most of our patients and their families had health and financial problems. Our social worker, Rorn-Ting Huang, found services to help them, such as nursing care and even financial help. So, we were lucky to be able to follow up all of our cases.

11. You state “Pathogens were isolated from CSF specimens in all patients” but this is redundant as it was required for study entry.

Response:
Thank you very much. This redundant sentence was omitted from the manuscript.

12. The CSF findings you required are very specific. How many patients were excluded as they grew Salmonella but did not fit the CSF criteria?

Response:
Thank you very much for your question. Actually, all of our 24 cases fit the CSF criteria in this study. There was none whose CSF grew Salmonella but did not fit the CSF criteria.
13. You state “Seizures were noted in 15 (63%) of the twenty-four patients before admission. Seizures occurred in thirteen (54%) during hospitalization”. What was the overlap in these two groups? This helps the reader to know how many children had no seizures.

**Response:**
Thank you very much for your suggestions. A sentence was added in the text to show how many patients had no seizures: “Six (25%) had no seizure noted in the course of *Salmonella* meningitis” (Page 9, Line 15).

14. In the sentence “CSF/blood glucose ratio < 0.5 was revealed in about 80% of those cases and CSF protein levels > 200 mg/dl in about a half of the patients”, I would reword to omit “revealed” and give the exact percentages rather than “about 80%” and “about half”. The latter is appropriate in a discussion but not in results. Also, one should not start a sentence with an abbreviation.

**Response:**
Thank you very much for your suggestions. The words “revealed in about” were omitted, and exact percentages were added to the sentence (Page 9, Line 17-18). In addition, Cerebrospinal fluid and its abbreviation were added (Page 9, Line 17).

15. Where you state “The twenty-four patients were treated with fourteen different antimicrobial regimens, and most received chloramphenicol or ampicillin in combination with one of the third generation antibiotics (cefotaxime, moxalactam, ceftriaxone, and ceftazidime)”, I think you mean “third generation cephalosporins”.

**Response:**
Thank you very much. The word “antibiotics” was replaced with cephalosporins in this sentence (Page 10, Line 2) and in Table 1.

16. For the patient who relapsed, it would be helpful to tell the reader which antibiotics they received for the 56 days. Also, it would be useful to mention what complication they had. It seems likely they had a complicated initial course if they were treated for 8 weeks.

**Response:**
Thank you very much for your suggestions. We gave more information for the clinical presentation of this case: “One case had acute complications, including refractory seizures, ventriculitis, and severe hydrocephalus, and received a ventriculoperitoneal shunt (Page 10, Lines 5-7)”.

17. Where you state “During hospitalization, brain sonography and/or CT scan and/or ventricular tap were performed to detect acute intracranial complications, and to diagnose ventriculitis. Those complications mainly included hydrocephalus (50%), subdural collection (42%), cerebral infarction (33%), ventriculitis (25%), empyema (13%), abscess (8%), and cranial nerve palsy (8%)”, I would omit “mainly” and list all complications if practical. I would clarify how many had sonography (N=?), CT (N=?) and ventricular tap (N=?). The reader will want to know if your percentages include all patients or just the ones with imaging.

Response:
Thank you very much for your suggestions. The word “mainly” was omitted from this sentence. The numbers of brain CT (N = 18), sonography (N = 22), and ventricular tap (N = 12) were added in this sentence (Page 10, Lines 10-11).

18. Top of Page 10 – “detailedly” is not a word. Spell-check should have found that if you used it.

Response:
Thank you very much. “Detailedly” is not a word and was omitted from the text.

19. When you present outcome data, I would begin by telling the reader how many children fell into each of the 5 categories you so nicely outlined in methods by stating as you do later: “Overall, good outcome was in six (28.6%) of twenty-one survivors, mild adverse outcome in three (14.2%), moderate in six (28.6%), and severe in six (28.6%).” I would say “Death occurred in 3 children (14.2%), good outcome in 6 (28.6 %) of twenty-one survivors, mild adverse outcome in 3 (14.2%), moderate adverse outcome in 6 (28.6%), and severe adverse outcome in 6 (28.6%). “

Response:
Thank you very much for your suggestion. This paragraph was presented in the beginning (Page 11, Line 6-10) of the section: Outcome of patients with Salmonella Meningitis for School-Age Survivors.

20. You need to provide definitions for “developmental delay” and “motor disabilities” in the methods if you are going to use these terms in the results as they mean different things to different readers.

Response:
Thank you very much for your suggestion. We provide the definitions for development delay and motor disabilities in the method section: “Developmental delay is defined as a child not reaching developmental milestones at the expected times, (Page 6, Lines 18-19)” and “Motor disability is defined as reduced ability to perform normal human motor functions, such as standing and walking.
(Page 7, Lines 2-3).”

21. Last sentence Page 11 – What do you mean by “consciousness change”? This is an awkward phrase. Again, a definition must be used in methods for any ambiguous term used in results.

Response:
Thank you very much for your suggestion. In our hospital, the modified Grady coma scale has been routinely used to measure the level of consciousness, classing children on a scale of I to V. The modified Grady coma scale was added in the method section (Page 6, Lines 9-12): “In this study, the modified Grady coma scale was used to measure the level of consciousness, classing children on a scale of I to V along a scale of lethargy or irritability (grade I), stupor (grade II), deep stupor (grade III), coma with abnormal posturing (grade IV), and coma without any response (grade V) [16].”

Discussion
22. There are lots of good ideas in this discussion. However, I would try to shorten the discussion by making each sentence more concise. I would present ideas in the following order:
- summary of findings
- compare your findings to other studies looking at outcome of Salmonella meningitis, providing some detail re the number of patients and length of follow-up in previous studies
- compare your outcome and that of other studies of Salmonella to outcome with other organisms, including a discussion of the prognostic factors you identified
- offer explanations for your high rate of poor outcome
- mention limitations of the study
- very brief conclusion about the practical take-home message for the reader and what further research should be done

Response:
We appreciate your very useful suggestions for a more structured discussion. We will do our best to edit the discussion section as you suggested.

23. In general, the discussion is less articulate than the rest of the article. You may want to have someone for whom English is a first language (even a non-medical person) help you with wording.

Response:
Upon your request, the manuscript has been proofread by a professional editor.
Table 1
24. The phrase “onset before admission” needs clarification. Do you mean “onset of symptoms before admission”?

Response:
Thank you very much for your correction. This phrase was changed to “onset of symptoms before admission”.

25. The phrase “clinical features at time of diagnosis” could maybe more accurately be called “clinical features present between onset of symptoms and day of diagnosis”

Response:
Thank you very much for your suggestion. This phrase was changed to “clinical features present between onset of symptoms and day of diagnosis”.

26. For “Salmonella isolates”, presumably not all samples were submitted on all 24 children. Please clarify.

Response:
Thank you very much. When a baby (≤ 1 year old) with a moderate to high degree of fever is sent to our hospital, the septic work-up of its admission is routinely performed, including routine examination and cultures of blood, stool, and urine specimens. In our children, the data of blood cultures were available in 22 cases; urine culture in 16 cases; stool cultures in 18 cases. The CSF cultures were performed in all our cases. The percentages of those items in parentheses were clarified in this table.

27. The term “disability” is vague. It needs to be defined in a footnote. One could put something like: “ongoing seizures (N=?), loss of motor milestones (N=?), etc.

Response:
Thank you very much for your valuable suggestions. The conditions of our cases at discharge were provided in this table. The term “disability” was defined in a footnote as “disability, impairment of physical ability and seizure”.

Table 2
28. Where possible, ranges should be provided for all parameters. It is way more useful for the reader to know if one ever has this diagnosis with no CSF pleocytosis than to know the mean number of CSF WBCs. What do you mean by “Positive Gram negative Rods”? It seems unlikely all Gram stains would be positive.

Response:
Thank you very much for your valuable suggestions.

1. The values in Table 2 have been presented as medians with interquartile ranges.
2. Gram stains and examination and culture of CSF are performed routinely for children who are suspected of CNS infection in our hospital. Bacteria come in different shapes, including round (cocci), oblong (rods) and spiral (spirilli). For instance, *Salmonella* and *E. coli* are rod-shaped. By gram stain, *Salmonella* and *E. coli* can be identified as “gram negative” and rod-shaped, presented as “gram negative rods”. To avoid confusion with “gram positive”, the word “positive” will be omitted from “positive gram negative rods”. Actually, the gram stains in our cases were all positive.

Table 3
29. Excellent table. I would also add in your 4 categories you outlined in the methods of good outcome, mild adverse outcome, etc.

**Response:**
Thank you very much for your excellent suggestions. Readers can easily get information of those 4 categories in the method section.

Table 4
30. You should use the same terminology you used in the methods for the outcomes (good, mild adverse, moderate adverse and severe adverse) instead of mild and major sequelae. Multivariate analysis using the parameters where p <0.10 would be very interesting.

**Response:**
Thank you very much for your suggestions. In this table, the word “major” was replaced with “moderate and severe” to enable readers to easily follow our study. Multivariate analysis is a very powerful test when you want to compare two or more variables among two or more groups. However the sample size is not enough to be analyzed by multivariate statistics analysis; it will decrease the power of the analysis. Therefore, 2-tailed Fisher’s exact test was used in the present study.