ORIGINAL ARTICLE

A retrospective cohort study comparing the cure rates of ampicillin, chloramphenicol, ampicillin and chloramphenicol combination, and third generation cephalosporins as initial antibiotic therapy for invasive *Haemophilus influenzae* infections

AUTHORS: Tomas T. Saiton, Jr., MD *

*Philippine Childrens' Medical Center

KEYWORDS:

invasive Hib disease, ampicillin, chloramphenicol, ampicillin-chloramphenicol combination, third generation cephalosporins, *Haemophilus influenzae*

CORRESPONDENCE:

Dr. Tomas Saiton

Email: tsaitonmd@yahoo.com

ABSTRACT

Background/Objective: *Haemophilus influenzae* type b remains to be a significant etiology of invasive infections specially in children two months to five years old without Hib vaccination. This study was performed to compare the cure rates of ampicillin, chloramphenicol, ampicillin-chloramphenicol combination and third generation cephalosporins as initial antibiotic treatments for documented invasive Hib infections. This study may assist in formulating recommendations on empiric antimicrobial therapy.

Methods: Charts of patients with invasive Hib disease confirmed either by blood culture, CSF culture and/or latex agglutination test from January 1991 to August 2010 were reviewed. Cases were classified into four groups depending on the initial antibiotic given upon admission. The four groups were compared and analyzed in terms of cure rates.

Results: The disease occurred predominantly in children less than two years old. Males were more frequently affected than females. All subjects were not given Hib vaccination. Cure rates were significantly different between ampicillin (33%) and chloramphenicol (89%) groups ($p=0.017$), and between chloramphenicol (89%) and ampicillin-chloramphenicol (39%) groups ($p=0.008$). However, cure rates were not significantly different when third generation cephalosporin group (62%) was compared to the other treatment groups ($p>0.05$). Resistance of Hib was 31% to ampicillin, while <10% to chloramphenicol and third generation cephalosporins.

Conclusion: Chloramphenicol is an excellent drug for empiric therapy in highly suspected or proven cases of invasive Hib disease.

INTRODUCTION

Haemophilus influenzae type b (Hib) causes pneumonia, occult bacteremia, meningitis, epiglottitis, septic arthritis, cellulitis, otitis media, purulent pericarditis, and other less common infections, such as endocarditis, endophthalmitis, osteomyelitis, and peritonitis. Non-type b encapsulated strains occasionally cause invasive disease similar to type b infections.[1]According to the Committee on Infectious Diseases of the American Academy of Pediatrics, before the introduction of effective Hib conjugate vaccines, Hib was the most common cause of bacterial meningitis in children in the United States.[1] Children between the ages of six-and-18 months are at highest risk for acquiring invasive Hib disease[2].

As a result of the introduction of Hib conjugate vaccines starting in 1987 in the United States for children 18 months of age and older (1990 for children 6 weeks of age or older), the incidence of invasive Hib disease has decreased by 99% to fewer than one case per 100,000 children younger than five years of age. The incidence of invasive infections caused by all other encapsulated and nontypeable strains combined is also low[1] In the United States, invasive Hib disease occurs primarily in underimmunized children and among infants too young to have completed the primary immunization series.[1]

In the Philippines and other resource-limited countries, Hib vaccines have just been recently included in the Expanded Program on Immunization (EPI). While Hib vaccines are already available in private clinics, majority still of Filipino children do not receive Hib vaccination due to financial constraints.

In the Philippine Pediatric Society (PPS) disease registry, there are 5,611 cases of meningitis (unspecified), and 6,920 cases of septicemia (unspecified) out of the 934,633 total cases reported from January 1, 2006 to August 31, 2010.[3] The results of local study done from 1994 to 1996 on the epidemiology of *H. influenzae* type b meningitis showed that 118 episodes of Hib meningitis were identified from among the population during the study period.[4] Sequelae occurred in 15% of the total cases, and the case fatality rate was 11%. The annual incidence of Hib meningitis in Manila for children less than five years old was 95 per 100,000.[4] There are no recent studies done on the treatments of invasive Hib infections .

The 2008 Antimicrobial Resistance Surveillance Program (ARSP) reported that 10% and 15% of Hib isolates were resistant to ampicillin and chloramphenicol, respectively.[5] Therefore, the program at that time, still recommended ampicillin as the best antimicrobial option for treating Hib infections in view of the increasing resistance rates to chloramphenicol.[5] The current (2012) ARSP data reported 16% and 8.2 % resistance to Ampicillin and Chloramphenicol respectively.[6] Thus Ampicillin is no longer recommended as a first line drug for this pathogen.

In the US, about 1/3 of the *H. influenzae* isolates produce B-lactamase and are therefore resistant to ampicillin.[6] According to the Committee on Infectious Diseases of American Academy of Pediatrics, initial therapy for children with meningitis caused by Hib is cefotaxime or ceftriaxone. Meropenem or the combination of ampicillin and chloramphenicol are alternative empiric regimens.[1]

A number of patients admitted at Philippine Children's Medical Center (PCMC) belong to the low-income group. Ampicillin and chloramphenicol are often used as empiric treatment for many infections due to its affordability. There is an increasing frequency of Hib infections with poor or non-response to initial antibiotics.

The purpose of this study is to analyze the clinical outcome of patients with invasive Hib diseases initially treated with either ampicillin alone, chloramphenicol alone, ampicillin and chloramphenicol combination, or third generation cephalosporins at PCMC.

MATERIALS AND METHODS

This is a retrospective cohort study.

Inclusion Criteria

Patients diagnosed with invasive Hib infections (sepsis and meningitis) by blood culture or CSF culture or Latex Agglutination Test (using the Remel Wellcogen* Bacterial Antigen Kit) who were seen and treated at PCMC between January 1, 1991 to August 31, 2010 were included in the study.

Exclusion Criteria

Patients with incomplete data (charts with missing laboratory results like CBC platelet, CSF analysis, blood and CSF culture or latex agglutination test) were excluded in the study. Patients with concomitant growth in the blood, CSF, pleural, pericardial, wound or other sites, as well as, positive latex agglutination test other than Hib were excluded.

Description of Study Procedure

Laboratory logbooks were checked and cases of culture or latex agglutination test positive for Hib infections between January 1, 1991 to August 31, 2010 were identified. The following data was obtained and recorded on case report forms: age, sex, address, period of hospital stay, final diagnosis, concomitant conditions for invasive Hib disease, clinical manifestations, CSF and neurosonographic findings, and presence of complications (e.g. hydrocephalus, subdural effusion or empyema, sensory or motor deficits).

Subjects were grouped based on the initial antibiotic given: Group I for ampicillin; Group II for chloramphenicol; Group III for ampicillin-chloramphenicol combination; and Group IV for third generation cephalosporin. Cure rates were assessed based on the effectiveness of an antibiotic with regard to clinical response (resolution of signs and symptoms of infection like fever and seizure), normalization of laboratory and microbiologic indices (repeat CBC platelet, CSF analysis and cultures) leading to patients' improvement or recovery and hospital discharge. The number and corresponding percentage of cases from each treatment group who were successfully treated using the initial antibiotic, who were subsequently discharged, who were shifted to other antibiotics were also determined and reasons for the shift of antibiotic (e.g. poor compliance /non-compliance, drug resistance, persistence fever, recurrence of seizure, development of subdural empyema, worsening of repeat CBC platelet or CSF parameters, drug reaction) from each treatment group were also analyzed and tabulated.

Data Analysis

The data collected were subjected to statistical analysis to determine if there were significant differences among treatment groups with reference to cure rate and mortality rate in the treatment of invasive Hib infections. Frequency distribution, mean and percentages were used for descriptive data. Pearson Chi-Square to test for relationship, Kruskal-Wallis Test, robust test of equality of means using Brown-Forsythe and Post Hoc Test using LSD for multiple comparisons were used.

RESULTS

Of 138 cases of *H. influenzae* type b invasive disease admitted at PCMC from January 1991 to August 2010, 78 charts were retrieved. Baseline characteristics of the subjects are seen in Table 1. All subjects had no history of Hib vaccination. Sixty-seven (93%) were admitted to service accommodation.

Table 2 shows the treatment outcome with ampicillin group. Out of nine cases who were given ampicillin as the initial antibiotic, only three (33%) responded and were eventually discharged. Five (55.5%) subjects in the ampicillin group were shifted to third generation cephalosporin. The most common reason for shifting was non-improvement in clinical parameters. Two (22.2%) subjects subsequently expired (one on ampicillin and another one after shifting to ceftriaxone).

Table 3 shows the treatment outcome with chloramphenicol group. Out of nine subjects given chloramphenicol as the initial antibiotic, eight (89%) responded and were subsequently discharged. Only one (11%) was

Table 1. Baseline Characteristics of Patients with Invasive Hib Disease.

Sex	Sepsis		Meningitis						Sepsis & Meningitis		N=72 (100%)
			LAT		CSF		LAT+CSF				
	N	Total =	N	Total =	N	Total =	N	Total =	N	Total =	
Male	8	8	18	34	9	15	7	10	3	5	45 (62.5%)
Female	0		16		6		3		2		27 (37.5%)
Percentage	11%		82% (N=59)						7%		
Age Group											
0-12 mos.	8		32		11		8		4		63 (87.5%)
13 – 24 mos.			2		3		2		1		8 (11.1%)
25 - 36 mos.					1						1 (1.4%)
37 mos. – up											0
TYPE OF ACCOMMODATION											
Service	8		33		14		8		4		67 (93%)
Pay			1		1		2		1		5 (7%)

Table 2. Diagnosis and Outcome of Patients with Invasive Hib treated with Ampicillin Alone

AMPICILLIN	SEPSIS	MENINGITIS			SEPSIS & MENINGITIS	TOTAL N=9	%
		LAT	CSF	LAT+CSF			
Clinical responders/Cure		3			0	3	33
Non-responders	1	2	1	2	0	6	67
a. Non or poor compliance						0	
b. Drug resistance	1			1		2	
c. No clinical improvement		2	1	2		5	
d. No improvement in lab or CSF parameters		2		2		4	
e. Drug reaction						0	
Ampicillin shifted to chloramphenicol						0	55.5
Ampicillin shifted to 3rd gen ceph	1	1	1	2		5	
Discharged	1	4	1	1		7	
Died		1		1		2	22.2

Table 3. Diagnosis and Outcome of Patients with Invasive Hib treated with Chloramphenicol Alone

CHLORAMPHENICOL	SEPSIS	MENINGITIS			SEPSIS & MENINGITIS	TOTAL N=9	%
		LAT	CSF	LAT+CSF			
Clinical responders/Cure	2	1	4	1	0	8	89%
Non-responders				1	0	1	11%
a. Non or poor compliance				1		1	
b. Drug resistance						0	
c. No clinical improvement				1		1	
d. No improvement in lab or CSF parameters						0	
e. Drug reaction						0	
Chloramphenicol shifted to 3rd gen ceph				1		1	11%
Discharged	2	1	3	2		8	
Died						0	0%
HAMA*			1			1	

*Home against medical advice

Table 4. Diagnosis and Outcome of Patients with Invasive Hib treated with Ampicillin-Chloramphenicol Combination

AMPICILLIN-CHLORAMPHENICOL COMBINATION	SEPSIS	MENINGITIS			SEPSIS & MENINGITIS	TOTAL N=33	%
		LAT	CSF	LAT+CSF			
Clinical responders/Cure		6	3	1	3	13	39
Non-responders		12	4	3	1	20	61
a. Non or poor compliance			1			1	
b. Drug resistance			1	3		4	
c. No clinical improvement		11	3	2		16	
d. No improvement in lab or CSF parameters		12	3	2	1	18	
e. Drug reaction						0	
Ampicillin-chloramphenicol shifted to third generation cephalosporin		11	4	3	1	19	57.6
Discharged		18	5	4	4	31	
Cases expired			1			1	3
HAMA*			1			1	

*Home against medical advice

Table 5. Diagnosis and Outcome of Patients with Invasive Hib treated with Third Generation Cephalosporins

THIRD GENERATION CEPHALOSPORIN	SEPSIS	MENINGITIS			SEPSIS & MENINGITIS	TOTAL N=21	%
		LAT	CSF	LAT+CSF			
Clinical responders/Cure	1	8	1	2	1	13	62
Non-responders	4	2	2			8	38
a. Non or poor compliance						0	
b. Drug resistance						0	
c. No clinical improvement	4	2	2			8	
d. No improvement in lab or CSF parameters	4	1				5	
e. Drug reaction							
Third generation shifted to other antibiotics (cefepime, meropenem, ciprofloxacin.)	3	2	1			6	28.6
Discharged	2	9	2	2	1	16	
Cases expired	2	1				3	14.3
HAMA*	1		1			2	

*Home against medical advice

shifted to ceftriaxone due to non-improvement according to the clinical parameters; this particular subject actually was not compliant to chloramphenicol. One subject also went home against medical advice. None (0%) of the subjects expired.

Table 4 shows the treatment outcome with ampicillin-chloramphenicol combination. Out of 33 subjects in the treatment group, 13 (39%) were responders and discharged, while 19 (61%) were shifted to third generation cephalosporin. The most common reason for shifting to other antibiotics was non-improvement in the laboratory and CSF parameters.

Table 5 shows treatment outcome with third generation cephalosporin. Out of 21 subjects started initially on ceftriaxone or cefotaxime, 13 (62%) responded and were discharged. Six (28.6%) were shifted to other antibiotics. Three (14.3%) cases expired.

Using the Kruskal-Wallis test, the percentage of patients responding to treatment in different treatment groups were found to be significant (p=0.03). This test was further supported by a robust test of equality of means, the Brown-Forsythe test (p=0.02). However, these two tests merely show the generalized difference among the four treatment groups, hence, a Post Hoc test for multiple comparisons using Least Significant Difference (LSD) pointed out the specific difference among these groups. It was noted that there were statistically significant difference between the ampicillin and chloramphenicol groups (p=0.017), and between chloramphenicol and ampicillin-chloramphenicol groups (p=0.008) with regard to cure rates. In contrast, the cure rate of the third generation cephalosporin group had no significant difference when compared to the cure rates of the other three treatment groups, as shown in the table below.

Table 6. Statistical Differences on Cure Rates Between Third Generation Cephalosporins and Other Treatment Groups

Third Generation cephalosporin 62%	Treatment Groups	Cure Rate	p value
	Ampicillin	33%	0.14
	Chloramphenicol	89%	0.163
	Ampicillin-chloramphenicol	39%	0.098

DISCUSSION

In PCMC, there were 138 cases of sepsis and meningitis secondary to Hib which were documented by blood and cerebrospinal fluid culture, and CSF latex agglutination test from January 1991 to August 2010. In this study, there was no decreasing pattern in the number of cases admitted at PCMC despite introduction of Hib vaccination in the private clinics. From 1991 to 2002, one-to-five cases per year were admitted at PCMC. An increase in the number of admissions was even noted in 2003 (8 cases) and 2004 (12 cases). However, the actual or exact burden of Hib invasive disease in the Philippines and in other countries in Asia and in the Western-Pacific geographic region may be underestimated. This could be due to factors such as intake of antibiotics prior to collection of specimens for blood and CSF cultures,[24] high cost of culture, sensitivity and latex agglutination tests, or even the unavailability of these tests in most centers. All subjects in this study did not receive a single dose of Hib vaccine. This reflects the poor economic and financial status of majority of Filipinos who cannot afford the Hib vaccine. Likewise, majority (93%) of subjects were admitted as service cases.

This study showed that cases of invasive Hib infections were more common in males (62.5%) and in zero-to-12 month old infants (87.5%). These observations also support the statements cited by the Committee on Infectious Diseases of AAP and by Ward [1,2]

The high cure rate of chloramphenicol noted in this study showed that this drug can still be effective in treating invasive Hib infections if cost and affordability are to be considered. Third generation cephalosporins are often preferred due to increasing resistance to ampicillin and chloramphenicol, as well as, to high rates of mortality and long-term morbidity associated with invasive Hib disease[24].

The lower cure rate of third generation cephalosporins over that of chloramphenicol (despite the the former's low resistance) may be due to many factors. The severity of illness upon admission (GCS score, need for intubation, presence of subdural effusion, empyema or hydrocephalus) of subjects to this study was not objectively classified. The number of subjects in this two treatment groups also differed. Thus, the zero mortality in the chloramphenicol group (N=9) was not statistically significant when compared to other treatment groups.

The cost of third generation cephalosporins has decreased in the Philippines, as well as, in many other countries because of cheaper generic drugs. The need to constantly monitor the quality of generic drugs circulating in the market is however very important since this can be one of the possible causes of treatment failure with third generation cephalosporins despite its low antimicrobial resistance.

The most common reason for the shift to other antibiotics in the ampicillin, chloramphenicol and third generation cephalosporin groups was non-improvement of clinical parameters. Shifting of antibiotics in ampicillin-chloramphenicol group, however, was due to non-improvement in laboratory and CSF parameters. The feared haematological side effects of chloramphenicol such as aplastic anemia and bone marrow depression, as well as, the increased incidence of diarrhea due to ceftriaxone seen in other studies were not noted in this study. Few cases on ceftriaxone were shifted to cefotaxime due to the consideration of drug fever.

The overall sensitivity and resistance patterns of antibiotics in this 20-year study period showed that Hib had the highest resistance to ampicillin (31%). The antimicrobial resistance to both chloramphenicol and third generation cephalosporin was still low (<10%). This data can somehow explain the lowest cure rate –seen in the ampicillin group. This study also showed that Hib resistance to cefepime and meropenem were also high at 25% and 20%, respectively. However, patterns of antimicrobial resistance are changing from period to period across different regions, thus the resistance noted in this study may not reflect therecentstatus.

The overall high resistance of Hib to ampicillin in this study supports the findings of Broker M., et al in the review of the burden of invasive Hib disease in Asia, which showed that in Bangladesh and Japan, resistance reached 32.5% and 60.1%, respectively.[24] However, the findings on chloramphenicol resistance were different. The same review revealed that resistance to chloramphenicol was also high (>20% -60%) in Bangladesh, India and Papua New Guinea.[24]

CONCLUSIONS

Cure rate was lowest (33%) in the ampicillin group, and highest (89%) in the chloramphenicol group. There was significant statistical difference between ampicillin and chloramphenicol groups, and between chloramphenicol and ampicillin-chloramphenicol groups with regard to cure rates. Though cure rate for third generation cephalosporin was also high (62%), there was no significant difference when this was compared to the cure rates of the other treatment groups.

Resistance of Hib to ampicillin was the highest (31%), while those of chloramphenicol and third generation cephalosporin were still below 10%, making these drugs still ideal antibiotics for empiric use. Chloramphenicol can be a good choice in patients with type 1 (anaphylactic type) hypersensitivity reaction to B-lactam antibiotics.

RECOMMENDATIONS

Further studies with larger sample size are recommended. Studies with same number of subjects with comparable demographic and clinical profile (duration of illness prior to admission, severity of illness before initiation of treatment, use of same antibiotics as to brands or manufacturers) per treatment group can

better assess and determine the cute rates and its statistical difference or significance without bias.

Chloramphenicol is a good drug for empiric therapy in highly suspected or proven cases of invasive Hib disease as shown in this study.

Hib remains to be an important pathogen causing invasive disease in children especially in the zero-to-12 month age group. Therefore, strict compliance to Hib vaccination should be observed.

REFERENCES

1. American Academy of Pediatrics. In: Pickering LK, Baker CJ, et al eds. Red Book: 2009 Report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village, IL: AAP; 2009: 314
2. Barenkamp SJ. Haemophilis Influenzae in Feigin, RD, Cherry JD, et al. Saunders Elsevier. Textbook of Pediatric Infectious Diseases. 6th ed. Vol. 2, Chapter 145, p. 1741
3. Philippine Pediatric Society. Committee on Registry of Childhood Disease (ICD-10). Philippine Council on Research and Publications. www.pps.org.ph. Sept 2010
4. Limcangco MR, Salole EG, et al. Epidemiology of *Haemophilus influenzae* type b Meningitis in Manila, Philippines, 1994 to 1996. Pediatr Infect Dis J 2000;19:7–11.
5. Carlos CC, et al. The Antimicrobial Resistance Surviellance Program (ARSP) Progress Report. Jan.-Dec. 2008.
6. Carlos CC, et al. The Antimicrobial Resistance Surviellance Program (ARSP) Progress Report. Jan.-Dec. 2013. Accessed from www.ritm.gov.ph.
7. 7. Abucejo-Ladesma E, Simoes EA, et al. Serious community-acquired paediatric infections in rural Asia (Bohol Island, Philippines): bacterial meningitis in children less than 5 years of age. Scand J Infect Dis 2007; 39:983-9. Epub 2007 Jun 21.
8. Vallejo JG, Kaplan SL, et al. Treatment of meningitis and other infections due to ampicillin-resistant *Haemophilus influenzae* type b in children. Rev Infect Dis 1991; 13(2):197-200.
9. Kristensen Kim, et al. Carriage and Antibiotic Susceptibility of *Haemophilus influenza* type b and non b in Danish Day-care Attendees. Acta Pathologica, Microbiologica et Immunologica Scandinavica 1990; 98: 50-52.
10. de Almeida AE, de Filippis I, et al. Antimicrobial susceptibility of *Haemophilus influenzae* isolates collected from four centers in Brazil (1990-2003). Diagn Microbiol Infect Dis 2006; 54(1):57-62. Epub 2005 Nov 14.
11. Ovalle MV, Agudelo CI, et at. Surveillance of *Haemophilus influenza* serotypes and Antimicrobial Resistance in Colombia, 1994-2002. Biomedica 2003; 23(2): 194-201
12. Saha SK, Baqui AH, et al. Invasive *Haemophilus influenzae* type b diseases in Bangladesh, with increased resistance to antibiotics. J Pediatr 2005; 146(2):227-33.
13. Nariai A, Hasegawa, et al. Prevalence of beta-lactamase-nonproducing ampicillin-resistant *Haemophilus influenzae* and *Haemophilus influenzae* type b strains obtained from children with lower respiratory tract infections. J Infect Chemother 2007; 13(6):396-9. Epub 2007 Dec 25.
14. Singh R, Thomas S, et al. Occurrence of multiple antimicrobial resistance among *Haemophilus influenza* type b causing meningitis. Indian J Med Res 1992; 95: 230-3.
15. 15. Peltola H, Anttila M, et al. Randomized comparison of chloramphenicol, ampicillin, cefotaxime, and ceftriaxone for childhood bacterial meningitis. Finnish Study Group. Lancet 1989; 1(8650):1281-7.
16. Barson WJ, Miller MA, et al. Prospective comparative trial of ceftriaxone vs. conventional therapy for treatment of bacterial meningitis in children. Pediatr Infect Dis 1985; 4(4):362-8.
17. del Rio MA, Chrane D, et al. Ceftriaxone versus ampicillin and chroramphenicol for treatment of bacterial meningitis in children. Lancet 1983; 1(8336):1241-4.
18. Congeni BL, et al. Comparison of ceftriaxone and traditional therapy of bacterial meningitis. Antimicrob Agents Chemother 1984; 25(1):40-4.
19. Aronoff SC, Reed MD, et al. Comparison of the efficacy and safety of ceftriaxone to ampicillin/chloramphenicol in the treatment of childhood meningitis. J Antimicrob Chemother 1984;13(2):143-51.
20. Camitta BM. The Anemias. W.B. Saunders Company. Nelson Textbook of Pediatrics, 15th Ed., Chapter 405, p. 1378, 1379
21. del Mundo F, Estrada FA, Santos Ocampo, PD, et al. Growth and Development. JMC Press, Inc. Textbook of Pediatrics and Child Health. 4th Ed., Chapter 3, p. 64-70.
22. Crawford SE, Daum RS, et al. *Haemophilus influenzae*. Saunders Elsevier. Nelson Textbook of Pediatrics, 18th Ed., Chapter 192, p. 1174
23. Llorin-Belleza MTS, Bibera GLG, et al. PPS Preventive Pediatric Health Care Handbook 2010. 6th Ed., p.
24. Broker, M. Burden of Invasive Disease Caused by *Haemophilus infuenzae* Type B in Asia Japan J Infect Dis 2009; 62: 87-92.