Acute Non-outbreak Shigellosis: Ten Years Experience in Southern Taiwan

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Background: We conducted a retrospective study of both the clinical and laboratory characteristics of shigellosis in southern Taiwan.

Methods: We collected shigella dysentery cases at Kaohsiung Chang Gung Memorial Hospital and Kaohsiung Veterans General Hospital from 1996 to 2005. Fifteen children and twelve adults were enrolled and their clinical presentations analyzed.

Results: Watery diarrhea (63.0%) was the most prevalent symptom in this study. Although the C-reactive protein (CRP) level was higher in patients with bloody diarrhea than those with watery diarrhea (123.5 ± 73.4 mg/L vs. 40.5 ± 36.7 mg/L, $p = 0.005$), there was no significant difference in the hospital stay ($p = 0.072$) and total number of days with fever ($p = 0.981$) between these 2 groups. The white blood cell (WBC) and neutrophil counts were significantly lower in patients with *Shigella flexneri* (*S. flexneri*) than those with *Shigella sonnei* (*S. sonnei*) enterocolitis ($p = 0.038$ and $p = 0.001$). WBC counts lower than 13,500/ mm^3 (OR = 3.17, 95% CI: 1.63-6.14, $p = 0.005$) and neutrophil counts lower than 9,400/ mm^3 (OR = 12.00, 95% CI: 1.16-123.68, $p = 0.030$) were more likely to be encountered in infections caused by *S. flexneri* than *S. sonnei*. Resistance was highest to trimethoprim-sulfamethoxazole (TMP-SMX) (56%), with ampicillin (28%) second. There was no significant difference between children and adults in total number of days with fever ($p = 0.532$), incidence of bloody diarrhea ($p = 1.000$), WBC count ($p = 0.177$), CRP level ($p = 0.858$), or hospital stay ($p = 0.734$).

Conclusion: Shigellosis should be considered in patients with watery diarrhea even without a contact history. There were lower blood WBC and neutrophil counts in *S. flexnei* than in *S. sonnei* enterocolitis. TMP-SMX and ampicillin should be used cautiously because of high resistance. There were no specific differences in the clinical and laboratory presentations between children and adults with shigellosis.

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Key words: shigellosis, watery diarrhea, bloody diarrhea, Kaohsiung

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Taiwan law requires that shigellosis be reported to health authorities, and 200 to 500 cases were identified annually from 1996 to 2004.[1,2] Epidemics usually occur in crowded areas with poor sanitary conditions where transmission from person to person is common, or when food or water is contaminated by the organism.[3-6] Despite the improved economy and public health, outbreaks of shigellosis are still reported in Taiwan.[1,7-10] However, between 1996 and 2005 there were no major outbreaks, with only sporadic cases in Kaohsiung.[2] In the United States, 74.4% of the infections are caused by *Shigella sonnei* (*S. sonnei*) and 13.6% by *Shigella flexneri* (*S. flexneri*), and the majority of cases (64.3%) are in children.[11] In Southeast Asia, 68% of cases are caused by *S. flexneri*, and the majority of cases (68.8%) are also in children.[12] In Taiwan, 73.3% of cases are reported to be caused by *S. sonnei* and 26.5% by *S. flexneri* and the majority (51%) of patients are also children.[2]

We retrospectively studied both the clinical and laboratory presentations of non-outbreak shigella dysentery with an effort to differentiate the characteristics in children and adults, and those younger and older than 5 years.

METHODS

Laboratory records of stool cultures for *Shigella* at two medical centers from January 1996 to December 2005 were reviewed. Chang Gung Memorial Hospital, Kaohsiung, a 2,500-bed tertiary referral medical center, and Veterans General Hospital, Kaohsiung, a 1,200-bed tertiary referral medical center, are both located in southern Taiwan. Of the 54,041 stool samples, 27 (0.05%) were positive for *Shigella* species and enrolled in this study.

An outbreak of shigellosis was defined as a significant increase in frequency in the same area, among a specified population, in the same season of the year. Diarrhea was defined as a decrease in consistency (i.e., soft or liquid) and an increase in frequency of bowel movements to 3 or more stools per day, as in other epidemiologic investigations.[13] Bloody stool was defined as any stool containing blood in the diarrhea period reported by the patient, parent, or guardian.[14] Fever was defined as a body temperature above 38°C; and bandemia as band forms [immature forms of white blood cells (WBC)] above 5%.

Antimicrobial susceptibility was examined by the disk diffusion method. The antimicrobial agents examined included ampicillin, ciprofloxacin, trimethoprim-sulfamethoxazole (TMP-SMX), and ceftriaxone, and susceptibility tests were performed on a routine-service basis. Susceptible and nonsusceptible isolates were defined according to the criteria suggested by the Clinical and Laboratory Standards Institute (CLSI, formerly National Committee for Clinical Laboratory Standards) of the United States.[15] Group 1 consisted of patients less than 5 years old and group 2 patients were older than 5 years. Related clinical features (clinical symptoms and signs, laboratory data, and length of hospitalization) were disclosed according to the chart records.

Data were presented as the mean ± standard deviation or median (range). The Mann-Whitney *U* test and X^2 test were used for the analysis. Statistical analyses were performed using the Statistical Package for Social Science (SPSS; version 10) software package. A p value of < 0.05 was considered statistically significant.

RESULTS

There was no outbreak except for a family with two cases in our study. There was one foreign wife from Vietnam but there was no specific travel history to outbreak areas in the charts reviewed. The case-year graph trend is shown in the Fig. 1. The overall clinical manifestations are shown in Tables 1 and 2. Twenty patients (74.1%) had fever, and bandemia occurred in 6 cases (22.2%). The children included 8 boys and 7 girls, and the age range was 11 months to 15 years old. The adults included 4 men and 8 women, and the age range was 20 to 76 years old.

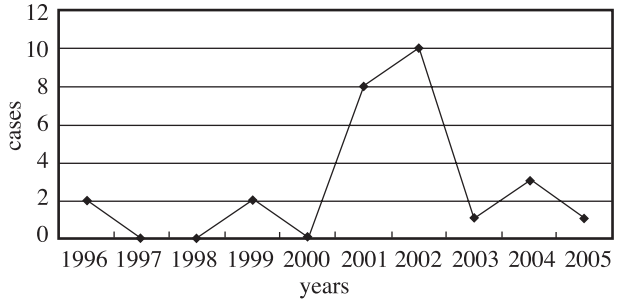

Fig. 1 Number of shigellosis cases, 1996-2005.

Table 1. Data on 27 Patients with Shigellosis

	Median	Range	Mean ± SD
Age (years)	13.5	0.9 – 76.0	21.3 ± 23.8
Hospital stay (days)	6.0	0 – 18.0	3.5 ± 5.9
Fever length (days)	3.0	0 – 14.0	3.0 ± 3.3
WBC count (/mm^3)	10,670	4,500 – 19,400	10,654 ± 4,142
Neutrophils (/mm^3)	7,574	2,642 – 15,850	6,405 ± 4,272
CRP (mg/L)	52.6	9.0 – 187.0	66.2 ± 66.5
Hb (g/dL)	12.6	10.0 – 15.0	12.8 ± 1.4
Platelets (x10,000/mm^3)	23.8	0.8 – 100.0	36.3 ± 17.6

Abbreviations: WBC: White blood cell; CRP: C-reactive protein; Hb: hemoglobin; SD: standard deviation.

Table 2. Comparison of Data between Patients Younger and Older than 5 Years

	≤ 5y/o (n = 10)	> 5 y/o (n = 17)	*p* value
Clinical data: (mean ± SD)			
Age (years)	2.6 ± 1.2	34.1 ± 23.5	< 0.001
Hospital stay (days)	5.6 ± 5.2	6.5 ± 6.5	0.729
Fever length(days)	4.4 ± 3.0	4.2 ± 3.7	0.874
WBC count (/mm^3)	12,838 ± 4,426	10,279 ± 3,762	0.128
Neutrophils (/mm^3)	9,158 ± 4,879	8,295 ± 3,782	0.664
Bands (%)	2.1 ± 3.9	4.3 ± 7.2	0.399
CRP (mg/L)	68.8 ± 66.2	77.6 ± 71.1	0.790
Hb (g/dL)	12.4 ± 1.4	12.7 ± 1.4	0.637
Platelets (x10,000/mm^3)	29.3 ± 11.7	27.3 ± 20.8	0.785
Clinical symptoms: n (%)			
Fever	8 (80%)	12 (70.6%)	0.678
Abdominal pain	4 (40%)	11 (64.7%)	0.257
Vomiting	5 (50%)	4 (23.5%)	0.065
Watery diarrhea	6 (60%)	11 (64.7%)	1.000
Bloody diarrhea	4 (40%)	6 (35.3%)	1.000
Seizures	0 (0%)	0 (0%)	–
Stool culture: n (%)			
S. flexneri	6 (60%)	7 (41.2%)	0.440
S. sonnei	3 (30%)	9 (52.9%)	0.424
S. boydii	1 (10%)	0 (0%)	0.370
S. dysenteriae	0 (0%)	1 (5.9%)	1.000

Abbreviations: WBC: White blood cell; CRP: C-reactive protein; Hb: hemoglobin; *S.: shigella;* SD: standard deviation.

There were no differences between the children and adults in the clinical and laboratory data, including total days with fever, (3.9 ± 2.6 vs. 4.9 ± 4.4 days, $p = 0.532$) , bloody diarrhea (6/15 vs. 4/12, OR: 1.33, 95% CI 0.27-6.50, $p = 1.000$), WBC count (12,291 ± 5,022 vs. 10,064 ± 2,503/mm^3, $p = 0.177$), C-reactive protein (CRP) level (74.3 ± 65.5 vs. 67.3 ± 80.4 mg/L, $p = 0.858$), and duration of hospital stay (6.6 ± 5.6 vs. 5.6 ± 6.4 days, $p = 0.734$). There were also no significant differences between those less than 5 years and older than 5 years old in either clinical manifestations or laboratory data (Table 2). But, there was a trend toward more vomiting symptoms in patients less than 5 years old ($p = 0.065$).

In the 27 cases, clinical bloody diarrhea occurred in 37.0% (n = 10) and watery diarrhea in 63.0% (n = 17) (Table 3). Stool analysis showed occult blood and pus cells in 23 cases, including 13 cases of watery diarrhea and all cases of bloody diarrhea. The CRP levels were higher in the bloody diarrhea group than the watery diarrhea group ($p = 0.005$). There were no significant differences between the bloody diarrhea and watery diarrhea groups in regard to hospital stay, other symptoms, and laboratory data (Table 3).

There were 13 cases of *S. flexneri,* 12 of *S. sonnei,* 1 of *Shigella dysenteriae* (*S. dysenteriae*), and 1 of *Shigella boydii* (*S. boydii*) (Table 2). All blood cultures grew no bacteria. A comparison between patients with *S. flexneri* and *S. sonnei* is shown in

Table 3. Comparison between Patients with Bloody Diarrhea and Watery Diarrhea

	Bloody diarrhea (n = 10)	Watery diarrhea (n = 17)	*p* value
Hospital stay (days)	7.1 ± 6.4	5.5 ± 5.6	0.072
Fever length (days)	4.3 ± 2.1	4.3 ± 3.9	0.981
CRP (mg/L)	123.5 ± 73.4	40.5 ± 36.7	0.005
WBC count (/mm^3)	10,927 ± 4,333	11,473 ± 4,147	0.751
Neutrophils (/mm^3)	6,782 ± 3,708	10,317 ± 4,182	0.064
Bands (%)	3.2 ± 5.4	3.6 ± 6.8	0.888
Hb (g/dL)	12.3 ± 1.5	12.7 ± 1.3	0.417
Platelets (x10,000/mm^3)	36.0 ± 25.2	23.1 ± 8.2	0.148

Abbreviations: WBC: White blood cell; CRP: C-reactive protein; Hb: hemoglobin.
Data presented as mean ± standard deviation.

Table 4. Resistance to TMP-SMX occurred in 56% (n = 14) of cases, ampicillin in 28% (n = 7), ceftriaxone in 0%, and ciprofloxacin in 0%. TMP-SMX and ampicillin resistance was higher with *S. flexneri* than *S. sonnei* (Table 4). Patients with *S. flexneri* infection had lower WBC and neutrophil counts (Table 4). *S. flexneri* infection was more likely than *S. sonnei* if the WBC count was lower than 13,500/ mm^3 (13/13 vs. 6/12, OR = 3.17, 95% CI: 1.63-6.14, $p = 0.005$), or if the neutrophil count was lower than 9,400/ mm^3 (12/13 VS. 6/12, OR = 12.00, 95% CI: 1.16-123.68, $p = 0.030$)

DISCUSSION

The annual incidence of shigella dysentery was 210 episodes per 100,000 people in South-East Asia,[12] 3.5 per 100,000 people in the United States,[11] and 2.4 per 100,000 people in Taiwan.[2] It was reported that the incidence of *Shigella* dysentery in Taipei and in Taiwan has decreased gradually.[2] Between 1996 and 2005, there was no outbreak except for some sporadic shigellosis cases in Kaohsiung.[2] However, this study did not show a decrease in shigellosis over the years, which is an important issue for public health in southern Taiwan. Immigration from South-East Asian countries has increased since 2004.[2] Kaohsiung is highly populated with laborers and overseas wives from South-East Asia.[2] These asymptomatic immigrants are suspected of being sources of transmission of shigellosis.[2,16,17] Another underlying predisposing cause may be travel and business, because of Kaohsiung's international harbor.[2]

Table 4. The Comparison between Patients with *S. flexneri* and *S. sonnei* Enterocolitis

	S. flexneri (n = 13)	*S. sonnei* (n = 12)	*p* value
Clinical and laboratory data: (mean ± SD)			
Age (years)	20.0 ± 23.5	21.6 ± 20.5	0.854
Hospital stay (days)	5.6 ± 6.6	6.8 ± 5.3	0.616
Fever length (days)	2.9 ± 2.3	4.2 ± 3.0	0.281
WBC count (/mm^3)	9,536 ± 2,767	13,115 ± 4,834	0.038
Segments (%)	67.0 ± 16.5	79.0 ± 7.4	0.030
Neutrophils (/mm^3)	6,746 ± 2,817	10,761 ± 4,311	0.001
Bands (%)	2.5 ± 4.9	2.8 ± 5.0	0.915
Hb (g/dL)	12.4 ± 1.4	12.6 ± 1.5	0.729
Platelets (x 10,000/mm^3)	26.6 ± 11.3	29.8 ± 23.7	0.670
CRP (mg/L)	67.5 ± 54.0	78.0 ± 80.2	0.748
Drug Resistance Rate: n (%)			
TMP-SMX	8 (61.5%)	6 (50%)	0.561
Ampicillin	6 (46.2%)	1 (8.3%)	0.073
Ciprofloxacin	0 (0%)	0 (0%)	–
Ceftriaxone	0 (0%)	0 (0%)	–

Abbreviations: WBC: White blood cell; CRP: C-reactive protein; Hb: hemoglobin; SD: standard deviation; TMP-SMX: trimethoprim-sulfamethoxazole.

Shigellosis is characterized by the passage of loose stool mixed with blood, accompanied by fever.[18] Only 37.0% of patients reported loose stool mixed with blood in our study as was also reported by Von Seidlein.[12] Bloody diarrhea contains visible blood and is a clinical diagnosis which indicates more severe infection[19] caused by invasion of colonic epithelial cells with mucosal ulcers.[18] Although the CRP level was higher in our bloody diarrhea cases, the hospital stay and total number of days with fever were not significantly different from the watery diarrhea cases. This may be due to the earlier use of antibiotics for cases with bloody diarrhea. Absence of visible blood can not be applied to exclude the diagnosis of shigellosis.

Shigella spp. includes *S. sonnei*, *S. flexneri, S. dysenteriae*, and *S. boydii*.[2,11,12] *Shigella* species of epidemic cases are different in developing and developed countries.[3,11,20-22] *S. flexneri* and *S. dysenteriae* are the most frequent causes in developing countries, but *S. sonnei* has been reported more often in developed countries.[3,11,20-22] In Taiwan, the prevalent species are *S. sonnei* and *S. flexneri*, and the rarest are *S. dysenteriae* and *S. boydii*.[2,23-25] Lin et al reported 47% of cases were caused by *S. Sonnei*, 41% by *S. flexneri*, and 3% by *S. dysenteriae* in Kaohsiung in 1992.[25] Our study was compatible with Lin's report.

Early initiation of antimicrobial therapy for patients with shigellosis in the course of the illness is necessary because this prompts a reduction in symptoms and excretion of the pathogens.[26] Many experts also believe that effective antimicrobial therapy for shigellosis may have a significant positive impact on the growth and nutritional status of affected children.[8,13] Ciprofloxacin is the preferred agent for shigellosis in adults,[27] but it is not recommended in pediatric patients because of the risk of damage to growing cartilage.[28] Drug resistance has become an important issue for shigellosis in rural areas in

Taiwan.[7,9,29] A 63% resistance to ampicillin and 59% resistance to TMP-SMX were reported in Oregon in the United States.[30] Likewise, there was a resistance of 10%-84% to ampicillin and 49%-92% to TMP-SMX in other South-East Asian countries.[12] In Taiwan, Lin et al. reported 52% of shigella strains were resistant to ampicillin and 10% to TMP-SMX.[25] Our data showed that TMP-SMX resistance was 56%, and ampicillin resistance 28%, with no resistance to ceftriaxone and ciprofloxacin. The susceptibility profiles of the *Shigella* isolates were similar to those identified in Kaohsiung 15 years ago.[25] In hospitalized children and adults with severe shigellosis, parenteral ceftriaxone or ciprofloxacin should be effective.[27]

Conclusions

Our study showed that shigellosis has not decreased in southern Taiwan. Furthermore, in southern Taiwan the diagnosis of shigellosis should not be excluded in those patients with watery diarrhea as the sole presentation. There were no differences in the clinical and laboratory manifestations of shigellosis between children and adults. There were lower blood WBC and neutrophil counts in *S. flexnei* than in *S. sonnei* enterocolitis. Because of high resistance rates to TMP-SMX and ampicillin in this area, early use of ceftriaxone or ciprofloxacin for suspected cases is recommended.

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非爆發流行性桿菌性痢疾的表現

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背 景： 研究南台灣在非爆發流行性桿菌性痢疾的臨床差異性及特性。

方 法： 收集高雄長庚紀念醫院及高雄榮民總醫院在 1996 年到 2005 年間的病例，共收集到 15 位孩童和 12 位大人，並加以分析其臨床症狀及檢驗數據。

結 果： 在我們的研究中未發現有桿菌性痢疾的爆發性流行。大部份 (63.0%) 都以水便來表現，但若以血便來表現的病人，其 C 反應蛋白比只以水便表現的病人爲高 (123.5 ± 73.4 mg/L vs. 40.5 ± 36.7 mg/L，p = 0.005)，但並不影響他們的住院天數 (p = 0.072)，或發燒天數 (p = 0.981)。*S. flexneri* 比 *S. sonnei* 感染病人有較低的白血球數及中性白血球數 (p = 0.038 and p = 0.001)，*S. flexneri* 感染病人白血球數小於 13,500/ mm^3 (OR = 3.17，95% CI: 1.63-6.14，p = 0.005) 及中性白血球數小於 9,400/ mm^3 (OR = 12.00，95% CI: 1.16-123.68，p = 0.030) 而非 *S. sonnei*。抗藥性最多爲 trimethoprim-sulfamethoxazole (TMP-SMX) (56%)，其次爲 ampicillin (28%)。但在大人與孩童在發燒天數 (p = 0.532)，血便的機率 (p = 0.722)，白血球數 (p = 0.177)，C 反應蛋白 (p = 0.858)，住院天數 (p = 0.734) 均無顯著差異。

結 論： 桿菌性痢疾並不能完全排除在單純水便的病人，*S. flexneri* 比 *S. sonnei* 感染病人有較低的血中白血球數及中性白血球數，使用 TMP-SMX 及 ampicillin 要注意抗藥性的問題，大人與孩童在臨床表現及檢驗值均無顯著差異。

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關鍵詞： 志賀氏桿菌，水便，血便，高雄

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