Journal of Microbiology, Immunology and Infection (2016) 49, 760—767

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Risk of recurrent nontyphoid *Salmonella* bacteremia in human immunodeficiency virus-infected patients with short-term secondary prophylaxis in the era of combination antiretroviral therapy

Yu-Ju Chou [a,b], Hui-Wen Lin [c], Chia-Jui Yang [c], Mao-Yuan Chen [a], Wang-Huei Sheng [a], Wen-Chun Liu [a], Sui-Yuan Chang [d,e,f], Chien-Ching Hung [a,g,h,*], Po-Ren Hsueh [a,d,e], Shan-Chwen Chang [a]

[a] *Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan*
[b] *Department of Internal Medicine, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan*
[c] *Department of Internal Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan*
[d] *Department of Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*
[e] *National Taiwan University College of Medicine, Taipei, Taiwan*
[f] *Department of Clinical Laboratory Science and Medical Biotechnology, National Taiwan University College of Medicine, Taipei, Taiwan*
[g] *Department of Medical Research, China Medical University Hospital, Taichung, Taiwan*
[h] *China Medical University, Taichung, Taiwan*

Received 27 March 2015; received in revised form 8 July 2015; accepted 15 July 2015
Available online 31 July 2015

KEYWORDS
AIDS-defining illness;
fluoroquinolones;
prevention;
septicemia;
trimethoprim-

Abstract *Background/Purpose:* Nontyphoid *Salmonella* (NTS) bacteremia causes high mortality and recurrence rates in human immunodeficiency virus (HIV)-infected patients. This study aimed to investigate the risk of recurrent NTS bacteremia in the era of combination antiretroviral therapy (cART).
Methods: The medical records of consecutive HIV-infected patients with NTS bacteremia from January 2006 to June 2014 were reviewed. The patients were divided into two groups: patients

* Corresponding author. Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 100, Taiwan.
E-mail address: hcc0401@ntu.edu.tw (C.-C. Hung).

http://dx.doi.org/10.1016/j.jmii.2015.07.005

sulfamethoxazole

who achieved a decline of plasma HIV RNA load by ≥ 2 $\log_{10}$ after 4 weeks of cART (good short-term virological response) and those who failed to achieve the goal (poor short-term virological response). Clinical information was collected on the demographics, immunological and virological responses, prophylactic antibiotics used, episodes of recurrent NTS bacteremia, and mortality.

Results: During the study period, 49 patients with 52 episodes of NTS bacteremia were included: 29 patients in the good virological response group, in which 16 received secondary prophylaxis; and 20 patients in the poor response group, in which 15 received secondary prophylaxis. There were no recurrent episodes of NTS bacteremia in the good-response group, whereas the incidence rate of recurrent NTS bacteremia was 5.21 per 100 person-years and 56.42 per 100 person-years of follow-up in patients receiving and not receiving prophylaxis, respectively, in the poor-response group. No patients died in the good-response group, whereas five patients (25%) in the poor-response group died. The resistance rate of 52 NTS isolates tested to ciprofloxacin was 7.7%.

Conclusion: The risk of recurrent NTS bacteremia is low in HIV-infected patients who achieve short-term virological response to cART, regardless of secondary prophylaxis.

Introduction

Bacteremia has been an important cause of morbidity and mortality in human immunodeficiency virus (HIV)-infected patients.[1–4] In developing countries, nontyphoid *Salmonella* (NTS) continues to be the leading cause of bacteremia that causes high mortality and recurrence rates.[4] According to the United States Centers for Disease Control and Prevention, recurrent NTS bacteremia is one of the AIDS-defining opportunistic infections.[5] After the introduction of combination antiretroviral therapy (cART), the incidence of bloodstream infections in HIV-infected patients has decreased with the improvement of immunologic status.[6] However, in patients with low CD4 lymphocyte counts, bacteremia, especially NTS bacteremia, remains a threat in developing countries.[1,2,4]

The guidelines of the United States Department of Health and Human Services in 2014 recommend that HIV-infected patients with recurrent gastroenteritis or NTS bacteremia, or those with CD4 counts $<$ 200 cells/μL and severe diarrhea receive secondary prophylaxis against recurrent NTS bacteremia.[9] However, the optimal duration of secondary prophylaxis for this purpose has not been well established, in contrast to the recommendations for primary and secondary prophylaxis against *Pneumocystis jirovecii* pneumonia. It is suggested to stop secondary prophylaxis until the resolution of *Salmonella* infection and response to cART with sustained viral suppression and CD4 cell count $>$ 200 cells/μL.[9] However, the prolonged exposure to antibiotics raises several concerns, such as drug toxicity and increasing antibiotic resistance. In our previous study, the incidence of NTS bacteremia has significantly decreased by 96% after the introduction of cART. Moreover, HIV-infected patients who received fluoroquinolones as secondary prophylaxis for $\leq$ 30 days did not experience a higher incidence of recurrent NTS bacteremia than those who received secondary prophylaxis for $>$ 30 days. However, the effectiveness of secondary prophylaxis with fluoroquinolones may be compromised given the finding that the proportion of NTS isolates resistant to fluoroquinolones has significantly increased over the three study periods.[8]

In this retrospective study, we aimed to reassess the risk of recurrent NTS bacteremia in the cART era. Our hypothesis is that in HIV-infected patients who receive cART with good adherence and a good short-term virological suppression, prolonged secondary prophylaxis for NTS bacteremia may not be needed.

Methods

Study design and inclusion and exclusion criteria

From January 2006 to June 2014, all HIV-infected patients who were aged 18 years or older and received a diagnosis of NTS bacteremia at the National Taiwan University Hospital, Taipei, Taiwan and Far Eastern Memorial Hospital, New Taipei City, were included in this retrospective observational cohort study. A standardized case record form was used to collect clinical and microbiological data. We excluded the patients who had to receive prolonged ($>$ 3 months) broad-spectrum antibiotics for other opportunistic infections, such as disseminated nontuberculous mycobacterial infections or recurrent pneumonia, because the prolonged use of antibiotics would interfere with the interpretation of the results of secondary prophylaxis against NTS bacteremia. We also excluded the patients who died during hospitalization when the first episode of NTS bacteremia developed, who were lost to follow-up within 2 months after the bacteremia, who had not received appropriate antibiotic treatment for NTS bacteremia, and who did not have sufficient laboratory data. The appropriate antibiotics for NTS bacteremia included a third- or

fourth-generation cephalosporin, or a fluoroquinolone that demonstrated *in vitro* activity against the NTS isolate tested.

The duration of secondary prophylaxis was defined as the duration of oral antibiotics after the patients had completed the 14-day course of effective parenteral antibiotic treatment. Recurrent NTS bacteremia was defined as blood cultures that yielded NTS $>$ 1 month after the discontinuation of antibiotic treatment or when the patient continued to receive antibiotic prophylaxis.

Rapid reduction of viremia in response to treatment was one of the important predictors of achieving long-term viral suppression.[7] Therefore, the patients included in the study were divided into two groups according to their short-term virological suppression status: the good virological suppression group, which included patients who achieved a decline of plasma HIV RNA load (PVL) by $\geq$ 2 $\log_{10}$ after taking 4 weeks of cART; and the poor virological suppression group, which included those who failed to achieve a decline of PVL by 2 $\log_{10}$. The patients in each group were further divided into two groups: those who received secondary prophylaxis against recurrent NTS bacteremia and those who did not.

Laboratory investigations

Isolation of *Salmonella* species was performed according to the standard methods from the blood samples. *Salmonella* serogroups B and D were further identified by the serotypes (Kauffman and White scheme), by using somatic and flagellar antigens (Denka Seiken Agglutinating Sera Salmonella Antisera Sets (Denka Seiken Co. Ltd., Tokyo, Japan)), and by conventional methods and the Phoenix System (panel type, NMIC/ID4; Becton Dickson). Disk diffusion susceptibility tests were performed for the *Salmonella* isolates, and results were interpreted according to the guidelines provided by the Clinical and Laboratory Standards Institute (formerly National Committee for Clinical Laboratory Standards).[10] Minimum inhibitory concentrations (MICs) of ampicillin, trimethoprim/sulfamethoxazole (TMP/SMX), ceftriaxone, and ciprofloxacin were determined using the agar dilution method or VITEK 2 microbial identification system (BioMérieux, Marcy-l'Etoile, France), according to the Clinical and Laboratory Standards Institute guidelines.[10] Both of the microbiology laboratories at the National Taiwan University Hospital and Far Eastern Memorial Hospital followed the same guidelines.

CD4 lymphocyte count was determined using flow cytometry (BD FACSCalibur, Becton Dickinson and Coulter Epics XL, Beckman Coulter, Brea, CA, USA). PVL was quantified using the Cobas AmpliPrep/Cobas TaqMan HIV-I test (version 2.0; Roche Molecular Systems, Inc.) with a lower detection limit of 20 copies/mL since June 2012.

Treatment and prophylaxis

During the study period, treatment of NTS bacteremia included parenteral administration of ceftriaxone or other third-generation cephalosporins, or a fluoroquinolone, that was administered for a 14-day course, followed by oral switch to ciprofloxacin administered at a dose of 500 mg twice daily or other newer fluoroquinolones as secondary prophylaxis. The duration of fluoroquinolone prophylaxis was at the discretion of treating physicians. All patients were recommended to start cART at the time when they received a diagnosis of HIV infection with AIDS according to the national HIV treatment guidelines of the Taiwan Centers for Disease Control.[11]

Data collection

A standardized case record form was used to collect the baseline information such as age, sex, white blood cell counts, CD4 cell count, and PVL in patients with NTS bacteremia. According to the national HIV treatment guidelines, second tests for CD4 cell count and PVL will be performed 4 weeks after the initiation of cART, which are performed every 3 months subsequently during the 1st year of cART. The duration of oral TMP/SMX for the prophylaxis of *P. jirovecii* infection was also recorded.

Statistical analysis

All statistical analyses were performed using SPSS statistical software (version 20.0; SPSS Inc., Chicago, IL, USA). The variables were compared using the Mann—Whitney *U* test. The patients were followed until December 31, 2014, death, or loss to follow-up, whichever occurred first. The incidence of recurrent NTS bacteremia was calculated as the number of episodes per 100 person-years of follow-up (PYFU). Exact 95% confidence intervals (95% CI) for incidence rates were calculated on the basis of the Poisson distribution. The resistance rates of fluoroquinolone were compared using the Mid-P exact tests.

Results

Patient characteristics

During the 8-year study period, 60 patients with 68 episodes of NTS bacteremia were identified (Figure 1). In seven episodes of NTS bacteremia, the patients died during the hospitalization course; the patients was lost to follow-up soon after four episodes; in two episodes, the patients had to receive prolonged broad-spectrum antibiotics for other reasons; in one episode, NTS bacteremia was diagnosed at an outpatient clinic for which the patient did not receive appropriate antibiotic treatment; and there were no sufficient data for two episodes. After excluding these 16 episodes, 49 patients who had 52 episodes of NTS bacteremia were included for analysis.

Except for one woman, all patients were male, with a median age of 33 years and 69.4% of them being younger than 40 years (Table 1). The median CD4 cell counts at the onset of NTS bacteremia were 30 cells/μL (range, 1—140 cells/μL). For treating NTS bacteremia, one patient received a fourth-generation cephalosporin, four patients received fluoroquinolones, and others had a third-generation cephalosporin. Twenty-nine patients (59.2%) were defined as having good short-term virological response to cART, and 20 patients (40.8%) were defined as having

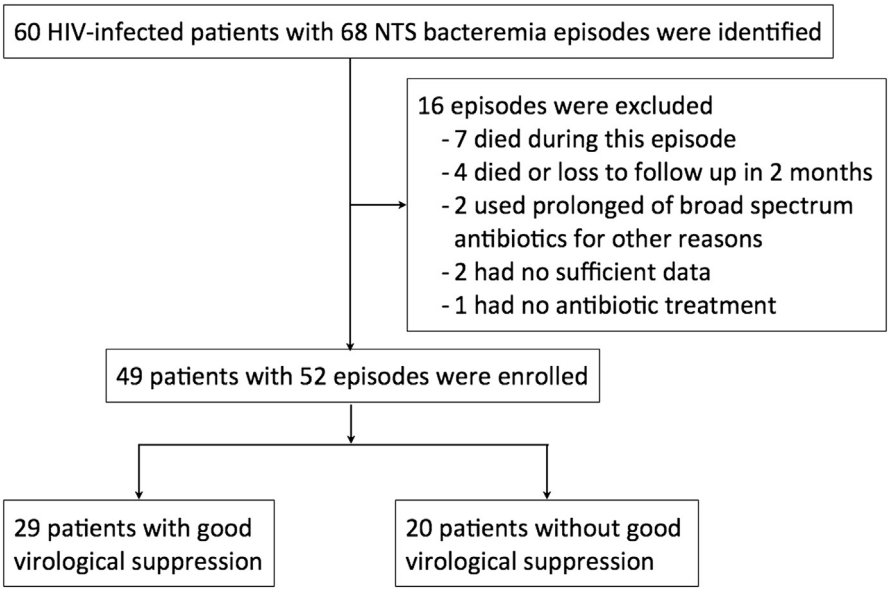

Figure 1. Disposition of patients with nontyphoid *Salmonella* (NTS) bacteremia.

poor short-term virological response. In the good virological response group, 16 patients received secondary prophylaxis and 13 did not receive prophylaxis, whereas in the poor virological response group, 15 patients received secondary prophylaxis and five did not receive prophylaxis. Twenty-four of the 49 patients (50.0%) also received TMP/SMX for the prevention of *P. jirovecii* pneumonia: 16 (16/29, 55.2%) in the good-response group (9 patients with secondary prophylaxis for NTS bacteremia and 7 without prophylaxis) and eight (8/20, 40.0%) in the poor-response group (6 patients with secondary prophylaxis for NTS bacteremia and 2 without prophylaxis). The median duration of TMP/SMX for primary or secondary prophylaxis for pneumocystosis was 28 days (range, 0—280 days) in the good-response group with prophylaxis and 0 day (range, 0—122 days) without prophylaxis; and 0 day (range, 0—154 days) in the poor-response group with prophylaxis and 0 day (range, 0—203 days) without prophylaxis (Table 1).

Immunological and virological responses

All but one patient received cART after the diagnosis of NTS bacteremia was made (Table 1). After 4 weeks of cART, the median CD4 cell count increased to 160 cells/μL (range, 12—772 cells/μL) in patients with good virological response, and 123 cells/μL (range, 3—615 cells/μL) in the poor-response group. The median follow-up duration was 1385 days (range, 330—3171 days) in the good-response group with prophylaxis and 584 days (range, 265—2968 days) without prophylaxis; and 506 days (range, 85—2826 days) in the poor-response group with prophylaxis and 526 days (range, 225—712 days) without prophylaxis (Table 2). At the end of follow-up, the median CD4 cell counts were 333 cells/μL (range, 21—731 cells/μL) in the good-response group and 61.5 cells/μL (range, 3—385 cells/μL) in the poor-response group (Table 1). In patients who had good virological response and received antibiotic prophylaxis, the CD4 cell counts at the end of follow-up were the highest among the four groups (median, 423 cells/μL; range, 80—691 cells/μL). Compared with patients with good virological response, the patients in the poor-response group, regardless of antibiotic prophylaxis for NTS bacteremia, had significantly lower median CD4 cell counts at the end of follow-up: with prophylaxis, 55 cells/μL (range, 3—385 cells/μL); without prophylaxis, 68 cells/μL (range, 3—139 cells/μL). The patients in the good-response group had a median increase of CD4 cell counts of 321 cells/μL (range, 5—678 cells/μL), whereas the CD4 count decreased by 4 cells/μL (range, −342—340 cells/μL) in the poor-response group.

The median baseline PVL was 5.38 $\log_{10}$ copies/mL (range, 4.3—6.97 $\log_{10}$ copies/mL) and 4.76 $\log_{10}$ copies/mL (range, 1.3—5.79 $\log_{10}$ copies/mL) in the good-response group and the poor-response group, respectively (Table 1). After 4 weeks of cART, the median decrease of PVL was 2.8 $\log_{10}$ copies/mL (range 2.09—3.7 $\log_{10}$ copies/mL) in patients with prophylaxis and 2.69 $\log_{10}$ copies/mL (2.15—4.04 $\log_{10}$ copies/mL) in those without prophylaxis in the good-response group, whereas it was 0.51 $\log_{10}$ copies/mL (range −3.49—1.98 $\log_{10}$ copies/mL) in patients with prophylaxis, and 0 $\log_{10}$ copies/mL (range −1.1—1.4 $\log_{10}$ copies/mL) in those without prophylaxis in the poor-response group.

Incidence and survival rate of recurrent NTS bacteremia

For the 16 patients who had good virological response and received secondary prophylaxis for NTS bacteremia, the median duration of prophylaxis was 19 days (range, 3—280 days), whereas for the 15 patients in the poor-response group who received prophylaxis, the median duration was 12 days (range, 2—52 days; Table 2). There were no recurrent episodes of NTS bacteremia in the good-response group, regardless of whether the patients received prophylaxis. In the poor virological response group, it was

Table 1 Characteristics of 49 human immunodeficiency virus (HIV)-infected patients with nontyphoid *Salmonella* bacteremia.

Variable	Good virological response		Poor virological response		All patients
	Prophylaxis	No prophylaxis	Prophylaxis	No prophylaxis	49
	16	13	15	5	
Age (y)	31.5 (22–53)	35 (29–50)	33 (23–64)	43 (26–52)	33 (22–64)
Male	16 (100)	13 (100)	14 (93.3)	5 (100)	48 (98)
WBC count at diagnosis (cells/μL)	5145 (2140–25,090)	4750 (2540–13,360)	4500 (2130–18,690)	5240 (3570–6470)	5130 (1540–25,090)
CD4, at diagnosis (cells/μL)	15.5 (4–71)	21 (9–410)	54 (1–386)	38 (7–138)	30 (1–410)
CD4, 4 wk after taking cART (cells/μL)	153.5 (23–276)	160 (12–772)	163 (3–615)	68 (17–139)	139 (3–772)
CD4, at the end of follow-up (cells/μL)	423 (80–691)	328 (21–731)	55 (3–385)	68 (3–139)	199 (3–731)
Increase of CD4 at the end of follow-up (cells/μL)	378 (20–678)	304 (5–647)	0 (−342–340)	−12 (−35–132)	167 (−342–678)
Log_{10} PVL, at diagnosis	5.34 (4.44–6.97)	5.38 (4.3–5.89)	3.68 (1.3–5.79)	5.02 (4.71–5.33)	5.24 (1.3–6.97)
Log_{10} PVL, 4 wk after taking cART	2.55 (1.3–4.02)	2.81 (1.3–3.46)	3.67 (1.3–5.58)	5.05 (3.83–5.91)	3.12 (1.3–5.91)
Decrease of log_{10} PVL	2.8 (2.09–3.7)	2.69 (2.15–4.04)	0.51 (−3.49–1.98)	0 (−1.1–1.41)	2.31 (−3.49–4.04)
Starting HAART after bacteremia,	16 (100)	13 (100)	15 (100)	4 (80)	48 (98)
Taking TMP/SMX	9 (56.3)	7 (53.8)	6 (40)	2 (40)	24 (50)
Duration of TMP/SMX (d)	28 (0 to 280)	0 (0–122)	0 (0–154)	0 (0–203)	0 (0–280)

Data are presented as *n* (%) or median (range).
cART = combination antiretroviral therapy; HAART = highly active antiretroviral therapy; PVL = plasma HIV RNA load; TMP/SMX = trimethoprim/sulfamethoxazole; WBC = white blood cells.

5.215 per 100 PYFU (95% CI, 0.8743–17.23) with prophylaxis, and 56.42 per 100 PYFU (95% CI, 17.93–136.1) without prophylaxis.

In the poor virological response group, two patients who received prophylaxis each developed one episode of recurrent NTS bacteremia (Table 2). In the no-prophylaxis group, a patient developed one episode and another patient developed three episodes of recurrent NTS bacteremia. There was no difference between the two subgroups (receiving or not receiving prophylactic antibiotics) in the good virological response group in the incidence of recurrent NTS bacteremia, nor was there any difference between the two groups of patients who received prophylactic antibiotics and achieved good response or those who failed to achieve good virological response ($p = 0.55$).

Serotypes of NTS isolates and the antimicrobial susceptibility

Of all 52 isolates, 44 were *Salmonella* O9 (serogroup D1) and five were *Salmonella* O4 (serogroup B; Table 2). In the good virological response group, three of the 29 isolates (10.3%) were resistant to ciprofloxacin, whereas in the poor-response group, one of the 23 isolates (4.3%) was resistant to ciprofloxacin. In patients receiving a fluoroquinolone for prophylaxis, either in good or poor virological response group, two out of 32 isolates (6.3%) were resistant to ciprofloxacin. In patients without fluoroquinolone prophylaxis, two out of 20 isolates (10.0%) were resistant to ciprofloxacin ($p = 0.653$). The overall resistance rate to ciprofloxacin for all 52 isolates was 7.7% (Table 2) and the resistance rate to ampicillin, ceftriaxone, and TMP/SMX was 44.2%, 1.9%, and 26.9%, respectively.

Characteristics of patients with recurrent NTS bacteremia

Four patients accounted for six episodes of NTS bacteremia. Their clinical characteristics are shown in Table 3. All four patients had baseline CD4 cell counts < 100 cells/μL and three had CD4 cell counts < 50 cells/μL. Patient 1 had three episodes of recurrent NTS bacteremia, and died during the third episode of recurrent NTS bacteremia. His CD4 cell count was 38 cells/μL, and he had a PVL of 51,000 copies/mL when the first episode occurred. He refused to start cART despite counseling. Other than NTS bacteremia, he had disseminated *Mycobacterium avium* complex infection and *P. jirovecii* pneumonia that led to death. Patient 2 had discontinued cART for 2 years prior to admission to the hospital for cryptococcal meningitis. The CD4 cell count was 41 cells/μL, and his PVL was 111,000 copies/mL. He did not receive secondary prophylaxis for NTS bacteremia. Recurrent NTS bacteremia developed when the CD4 count decreased to 18 cells/μL. He died of cerebral septic embolism, which occurred after he received chemotherapy for subsequent anaplastic large-cell lymphoma. Patient 3 discontinued cART despite the fact that his CD4 cell count had fallen to 1 cell/μL and his PVL was 62,300 copies/mL. Ciprofloxacin was prescribed for 28 days for secondary prophylaxis. However, recurrent NTS

Table 2 Outcome of recurrence of nontyphoid *Salmonella* bacteremia, survival, and antibiotics resistance.

Variable	Good virological response		Poor virological response	
	Prophylaxis ($n = 16$)	No prophylaxis ($n = 13$)	Prophylaxis ($n = 15$)	No prophylaxis ($n = 5$)
Duration of secondary prophylaxis (d)	19 (3–280)	0	12 (2–52)	0
Follow-up duration (d)	1385 (330–3171)	584 (265–2968)	506 (85–2826)	526 (225–712)
Having recurrent NTS bacteremia	0	0	2	2
Episodes of recurrent NTS bacteremia	0	0	2	4
Incidence, per 100 PYFU (95% CI)	0	0	5.215 (0.8743–17.23)	56.42 (17.93–136.1)
Survived	15 (39.8)	11 (84.6)	9 (60)	1 (20)
Died	0	0	2 (13.3)	3 (60)
Lost to follow-up	1 (6.3)	2 (15.4)	4 (26.7)	1 (20)
Isolates	16	13	16	7
Salmonella O9 (Group D1)	15 (93.8)	8 (61.5)	15 (93.8)	6 (85.7)
Salmonella O4 (Group B)	1 (6.3)	2 (15.4)	1 (6.3)	1 (14.3)
Antimicrobial susceptibility				
Resistant to ampicillin	6 (37.5)	8 (61.5)	8 (50)	1 (14.3)
Resistant to ciprofloxacin,	2 (12.5)	1 (7.7)	0	1 (14.3)
Resistant to ceftriaxone	0	1 (7.7)	0	0
Resistant to TMP/SMX	5 (31.3)	2 (15.4)	6 (37.5)	1 (14.3)

Data are presented as *n*, *n* (%), or median (range).
95% CI = 95% confidence interval; NTS = nontyphoid *Salmonella* bacteremia; PYFU = person-years of follow-up; TMP/SMX = trimethoprim/sulfamethoxazole.

bacteremia developed 2 months after his discharge from the hospital, and he subsequently died of *P. jirovecii* pneumonia. Patient 4 had poor adherence to cART and presented with *P. jirovecii* pneumonia, HIV nephropathy with nephrotic syndrome, and cytomegalovirus pneumonitis when NTS bacteremia occurred. NTS bacteremia recurred despite ciprofloxacin prophylaxis. He subsequently died of respiratory failure.

Discussion

In this study, we found that HIV-infected patients who had good short-term virological response to cART that was defined as a decline of PVL of $\geq$2 $\log_{10}$ after 4 weeks of cART were at a low risk of having recurrent NTS bacteremia. Regardless of the use of secondary prophylactic antibiotics, none of the 29 patients on cART with short-term virological response developed recurrent NTS bacteremia.

NTS is an important etiology of bacterial infection in immunocompromised hosts and infants in Taiwan,[12,13] and the leading cause of bacteremia in patients with advanced HIV infection.[14] The incidence of recurrent NTS bacteremia of patients without prophylaxis and poor virological suppression in the current study (56.42 per 100 PYFU) is lower than that in the pre-cART era in our previous report (70.56 per 100 PYFU).[8] The decrease may be related to the partial treatment effect of cART. For patients with good virological control, there was no recurrence of NTS bacteremia in this study (which was conducted between 2006 and 2014) compared with the incidence of 2.56 per 100 PYFU in our previous study (1997–2006).[8] Twenty-eight of the 49 patients (57.1%) were antiretroviral-naïve at the first episode of NTS bacteremia, and 42 patients (85.7%) either started cART or had changes made to the antiretroviral regimens after the episodes of NTS bacteremia. These findings highlight the importance of early diagnosis of HIV, early initiation of cART, and retention of the patients in the HIV care system for the prevention of recurrent NTS bacteremia. With good virological suppression, the role of secondary prophylaxis for NTS bacteremia may be minimized. Our findings suggest that, regardless of the baseline CD4 cell count, for patients who start cART with good adherence and virological response, prophylactic antibiotics for the prevention of recurrent NTS bacteremia may not be needed.

Patients with a low CD4 cell count are at high risk of NTS bacteremia.[15] In our previous study, we found that patients with NTS bacteremia had depleted CD4 cell counts [median, 8 cells/μL and 20 cells/μL in the pre-highly active antiretroviral therapy (HAART) and post-HAART era, respectively].[8] In this study, the patients with poor virological suppression continued to have lower CD4 cell counts at the end of follow-up (median CD4 cell count, 55 cells/μL and 68 cells/μL in patients with prophylaxis and those without prophylaxis, respectively). By contrast, patients with good virological suppression had significant increases of CD4 counts to 423 cells/μL and 328 cells/μL in patients with prophylaxis and those without prophylaxis, respectively. The CD4 cell counts at the end of follow-up of the four patients who had recurrent NTS bacteremia were all $<$ 50 cells/μL. This suggests that a poor immunological recovery and poor adherence to cART and secondary prophylaxis prescribed may have contributed to the higher incidence of recurrent NTS bacteremia observed.[8]

In the good virological response group, nine patients received a prophylactic dose of TMP/SMX for pneumocystosis in addition to a fluoroquinolone, and seven patients received TMP/SMX without other antibiotics. None of the patients in both groups developed recurrent NTS

Table 3 Clinical and laboratory characteristics of the four patients with recurrent nontyphoid *Salmonella* bacteremia.

Patient	1	2	3	4
Age (y)/Sex	43/M	30/M	23/M	37/M
Recurrent episodes	3	1	1	1
Salmonella serotype	O9, serogroup D1	O9, serogroup D1	O9, serogroup D1	O9, serogroup D1
Risk for HIV infection	Unknown	MSM	Unknown	MSM
Baseline CD4 count (cells/μL)	38	29.6	1	71
CD4 count at 4 wk of cART (cells/μL)	17	34.2	1	174
CD4 count at the end of follow-up (cells/μL)	3	17.5	3	40.5
Baseline PVL (copies/mL)	51,000	64,900	623,000	111,000
PVL at 4 wk of cART (copies/mL)	51,000	818,000	376,000	4630
Secondary antibiotic prophylaxis	None	None	Levofloxacin	Ciprofloxacin
Duration of prophylaxis (d)	0	0	20	12
Duration of TMP/SMX (d)	0	203	0	0
Other OIs	Disseminated MAC infection, PJP	Cryptococcal meningitis	PJP, pulmonary TB	PJP, oral candidiasis
Follow-up duration (d)	526	433	67	85

cART = combination antiretroviral therapy; MAC = *Mycobacterium avium* complex; MSM = men who have sex with men; OI = opportunistic infection; PJP = *Pneumocystis jirovecii* pneumonia; PVL = plasma HIV RNA load; TMP/SMX = trimethoprim/sulfamethoxazole; TB = tuberculosis.

bacteremia. In the poor-response group, six patients and two patients received TMP/SMX with and without a secondary prophylactic antibiotic, respectively. Only one of four patients with recurrences (Patient 3) received TMP/SMX, with poor adherence. In our study, the resistance rate to TMP/SMX among these 52 isolates was 27.0%. With such a high resistance rate, whether receiving TMP/SMX is effective or the dose administered for preventing recurrent NTS bacteremia is appropriate remains unknown. Furthermore, the multiple adverse effects related to TMP/SMX may limit its prolonged use in the HIV-infected population.[16]

In African adults and children, the estimated mortality rate associated with NTS bacteremia was 20—25%.[17] In our study, no patient died in the good virological response group, whereas five patients (25%) died in the poor virological response group: two received antibiotic prophylaxis and three did not. However, none of these five patients died of NTS bacteremia, but of other opportunistic infections or complications. This finding suggests that the recurrence of NTS bacteremia could be a marker of poor treatment response or adherence to cART, and the patients remain at a significantly higher risk for other coexistent life-threatening opportunistic illnesses.

In our study, 44 of the 52 (84.6%) NTS isolates were *Salmonella* O9 (Group D1) and five (9.6%) were *Salmonella* O4 (Group B). In another single-center study of NTS bacteremia in both HIV-infected and non-HIV patients in northern Taiwan, serogroup D was also the most prevalent serogroup, followed by serogroup B (23.4%), serogroup C2 (6.3%), and serogroup C1 (1.6%).[12] The resistance rate to ciprofloxacin of the 52 isolates tested was 7.7%. In our previous study,[8] it was 0% in the pre-HAART era (from June 1994 to March 1997), which increased from 6.2% in the early cART era (from April 1997 to June 2002) to 34.2% in the late cART era (from July 2002 to June 2006). The causes of the observed decrease in NTS with resistance to ciprofloxacin remain to be investigated, although shortened use of fluoroquinolones in the prevention of secondary NTS bacteremia may theoretically reduce the selection pressure for the emergence of antimicrobial resistance.

Our study had several limitations. First, the number of patients is small. In view of a low incidence of recurrent NTS bacteremia in the modern cART era, comparative clinical trials of a large sample size are necessary to assess the efficacy of a short course versus longer course of prophylaxis against recurrences. Second, this is a descriptive study. Owing to the small number of patients included, the study was underpowered to demonstrate statistically significant differences in several comparisons between groups. Third, unlike our previous study,[8] we did not perform molecular typing of the *Salmonella* isolates to differentiate relapse from reinfection with NTS. Last, the patients who had poor virological response might have been infected with HIV-1 with pretreatment resistance or emergence of drug resistance mutations to the antiretroviral regimens administered; however, we did not have the data on the baseline and follow-up resistance mutations of the HIV-1 strains.

In conclusion, HIV-infected patients who achieve good short-term virological response to cART are at a low risk of having recurrent NTS bacteremia, and a prolonged course of secondary prophylactic antibiotics may not be needed.

Conflicts of interest

All authors have no conflicts of interest to declare.

Acknowledgments

This study was supported by grants from the Centers for Disease Control, Taiwan (grant numbers DOH102-DC-1401 and MOHW103-CDC-C-114-000405 to C.-C.H.). The funding source had no role in study design and conduct; data collection, analysis, or interpretation; or in the writing of the manuscript or the decision to submit it for publication.

References

1. Gilks CF, Brindle RJ, Otieno LS, Simani PM, Newnham RS, Bhatt SM, et al. Life-threatening bacteraemia in HIV-1 seropositive adults admitted to hospital in Nairobi, Kenya. *Lancet* 1990;**336**:545—9.
2. Vugia DJ, Kiehlbauch JA, Yeboue K, N'Gbichi JM, Lacina D, Maran M, et al. Pathogens and predictors of fatal septicemia associated with human immunodeficiency virus infection in Ivory Coast, West Africa. *J Infect Dis* 1993;**168**:564—70.
3. Gordon MA, Walsh AL, Chaponda M, Soko D, Mbvwinji M, Molyneux ME, et al. Bacteraemia and mortality among adult medical admissions in Malawi—predominance of non-typhi salmonellae and Streptococcus pneumoniae. *J Infect* 2001; **42**:44—9.
4. Gordon MA, Banda HT, Gondwe M, Gordon SB, Boeree MJ, Walsh AL, et al. Non-typhoidal salmonella bacteraemia among HIV-infected Malawian adults: high mortality and frequent recrudescence. *AIDS* 2002;**16**:1633—41.
5. Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep* 1992;**41**:1—19.
6. Pedro-Botet ML, Mòdol JM, Vallés X, Romeu J, Sopena N, Giménez M, et al. Changes in bloodstream infections in HIV-positive patients in a university hospital in Spain (1995—1997). *Int J Infect Dis* 2002;**6**:17—22.
7. U.S. Department of Health and Human Services. *Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents*. 2014.
8. Hung CC, Hung MN, Hsueh PR, Chang SY, Chen MY, Hsieh SM, et al. Risk of recurrent nontyphoid *Salmonella* bacteremia in HIV-infected patients in the era of highly active antiretroviral therapy and an increasing trend of fluoroquinolone resistance. *Clin Infect Dis* 2007;**45**:e60—7.
9. Powderly WG, Saag MS, Chapman S, Yu G, Quart B, Clendeninn NJ. Predictors of optimal virological response to potent antiretroviral therapy. *AIDS* 1999;**13**:1873—80.
10. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing: Twenty-Forth Informational Supplement. M100—S24*. Wayne, PA: Clinical and Laboratory Standards Institute (CLSI); 2014.
11. Centers for Disease Control. *Guidelines for diagnosis and treatment for HIV/AIDS*. 4th ed. Taiwan: Centers for Disease Control; 2013.
12. Lin HW, Hsu HS, Huang YT, Yang CJ, Hsu MS, Liao CH. Time to positivity in blood cultures of adults with nontyphoidal *Salmonella* bacteremia. *J Microbiol Immunol Infect* 2016;**49**: 417—23.
13. Ting YT, Lu CY, Shao PL, Lee PI, Chen JM, Hsueh PR, et al. Epidemiology of community-acquired bacteremia among infants in a medical center in Taiwan, 2002—2011. *J Microbiol Immunol Infect* 2015;**48**:413—8.
14. Hung CC, Hsueh PR, Hsieh SM, Liu CJ, Chen MY, Luh KT. Bacteremia and fungemia in patients with advanced human immunodeficiency virus (HIV) infection in Taiwan. *J Formos Med Assoc* 1998;**97**:690—7.
15. Thamlikitkul V, Dhiraputra C, Paisarnsinsup T, Chareandee C. Non-typhoidal *Salmonella* bacteraemia: clinical features and risk factors. *Trop Med Int Health* 1996;**1**:443—8.
16. Yang JJ, Huang CH, Liu CE, Tang HJ, Yang CJ, Lee YC, et al. Multicenter study of trimethoprim/sulfamethoxazole-related hepatotoxicity: incidence and associated factors among HIV-infected patients treated for *Pneumocystis jirovecii* pneumonia. *PLoS ONE* 2014;**9**:e106141.
17. Feasey NA, Dougan G, Kingsley RA, Heyderman RS, Gordon MA. Invasive non-typhoidal salmonella disease: an emerging and neglected tropical disease in Africa. *Lancet* 2012;**379**: 2489—99.