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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*

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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).

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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