

# Nontyphoidal *Salmonella* bacteremia in antiretroviral therapy-naïve HIV-infected individuals at three public hospitals in Eastern Ethiopia: prevalence, antimicrobial susceptibility patterns, and associated factors

Habtamu Mitiku  
Fitsum Weldegebreal  
Dadi Marami  
Zelalem Teklemariam

Department of Medical Laboratory  
Sciences, College of Health and  
Medical Sciences, Haramaya  
University, Harar, Ethiopia

**Background:** Nontyphoidal *Salmonella* bacteria have emerged as the prominent cause of severe and life-threatening bacteremia in HIV-infected patients. Antimicrobial resistance is another concern that adversely affects the health outcome of the patients. This study investigated the prevalence, antimicrobial susceptibility pattern of the isolates, and associated factors of nontyphoidal *Salmonella* bacteremia among antiretroviral therapy-naïve HIV-infected adult individuals at three public hospitals in Eastern Ethiopia.

**Methods:** A cross-sectional study was conducted among 170 antiretroviral therapy-naïve HIV-infected adult individuals in three public hospitals in Eastern Ethiopia from June 2017 to June 2018. Data on sociodemographic and associated factors were collected using a pretested structured questionnaire. Blood specimens were examined for nontyphoidal *Salmonella* using the recommended culture and serological methods. Data were analyzed using the Statistical Package for Social Sciences version 20.0. Bivariate and multivariate logistic regression models were used to identify the predictors of nontyphoidal *Salmonella* bacteremia. A *P*-value <0.05 was considered as statistically significant.

**Results:** The prevalence of nontyphoidal *Salmonella* bacteremia was 10% (95% CI: 5.93–15.54). A lack of hand washing habit before food preparation (adjusted odds ratio [AOR]: 13.1, 95% CI: 10.40–15.30) and a CD4<sup>+</sup> count <200 cells/μL (AOR: 3.61, 95% CI: 1.74–5.25) were found to be significantly associated with nontyphoidal *Salmonella* bacteremia. Most isolates were sensitive to gentamycin (76.5%), ciprofloxacin (70.5%), and ceftriaxone (58.8%), but resistant to tetracycline (88.2%), chloramphenicol (76.5%), ampicillin (70.6%), and sulfamethoxazole–trimethoprim (70.6%).

**Conclusion:** The prevalence of nontyphoidal *Salmonella* bacteremia was high. HIV-infected patients who did not wash their hands before food preparation and those whose CD4<sup>+</sup> count was <200 cells/μL had significantly higher odds of nontyphoidal *Salmonella* bacteremia. Tetracycline, chloramphenicol, ampicillin, and sulfamethoxazole–trimethoprim should not be used for the treatment of nontyphoidal *Salmonella* bacteremia. The treatment needs to be supported by culture isolation and antimicrobial susceptibility tests.

**Keywords:** prevalence, salmonellosis, HIV/AIDS, immunosuppression, drug resistance, Ethiopia

Correspondence: Dadi Marami  
Department of Medical Laboratory  
Sciences, College of Health and Medical  
Sciences, Haramaya University, PO Box  
235 Harar, Ethiopia  
Tel +251 025 666 18 86  
Fax +251 025 666 80 81  
Email dmarami4@gmail.com

## Background

*Salmonella* species are capable of causing typhoidal illness,<sup>1</sup> while some of them cause nontyphoidal *Salmonella* (NTS) infection. NTS is generally limited to the intestine,

causing self-limiting gastroenteritis in immunocompetent individuals.<sup>2</sup> In HIV-infected patients, it spreads to the bloodstream and causes an aggressive and life-threatening systemic infection, collectively known as invasive NTS infection or bacteremia.<sup>3,4</sup> Depletion of CD4<sup>+</sup> T-cells and associated interleukin-17-producing T-cells (Th17 cells) in gastrointestinal mucosa that control local invasion,<sup>3,5</sup> reduction of the cytokines production that are vital for the killing of intracellular *Salmonella*, and dysfunction of antibodies responsible for serum and intracellular oxidative killing of invasive *Salmonella* can probably explain its pathogenesis.<sup>6,7</sup> The modes of transmission in limited-resource countries are less well understood.<sup>2</sup>

Nontyphoidal *Salmonella* continues to be the leading cause of high mortality and recurrence bacteremia in developing countries and is now an emerging disease among HIV-infected patients in sub-Saharan Africa.<sup>4,8</sup> It is typically presented in patients with HIV once the level of CD4<sup>+</sup> count falls <200 cells/ $\mu$ L.<sup>9</sup> In sub-Saharan Africa, it is responsible for the hospitalization of 1.9 million immunosuppressed individuals<sup>3,6</sup> with an overall estimated incidence rate of 2,000–7,500 cases per 100,000 HIV-infected adult patients.<sup>10</sup> Despite the substantial burden of illness and death, much remains to be done to understand and control NTS bacteremia in sub-Saharan Africa.<sup>11</sup>

Antimicrobial-resistant *Salmonella* has arisen across the globe as a consequence of widespread antibiotic consumption.<sup>2</sup> Particularly, the resistance to commonly used antimicrobial agents for the treatment of NTS bacteremia in developing countries, where there are limited health care facilities, is of major concern.<sup>3,12,13</sup> The resistance often arises as a result of selective pressure antimicrobials because of overprescribing by health professionals for several health problems, patient self-medication, and noncompliance with recommended treatment.<sup>14,15</sup>

Nontyphoidal *Salmonella* bacteremia in HIV-positive individuals is recognized as an AIDS-related opportunistic infection<sup>16</sup> and is therefore incorrectly diagnosed, unreported, or not sufficiently studied in developing countries.<sup>3,13,17</sup> Information on NTS bacteremia in HIV-infected individuals is limited in Ethiopia. This study describes the prevalence, antimicrobial susceptibility pattern of isolates, and associated factors of NTS bacteremia among antiretroviral therapy (ART)-naïve HIV-infected adult individuals at three public hospitals in Eastern Ethiopia.

## Materials and methods

### Study area and period

This study was conducted at Hiwot Fana Specialized University Hospital, Jugal Hospital, and Dilchora Hospital from June 2017 to June 2018. The former two hospitals are located

in Harar town 525 km from Addis Ababa, Eastern Ethiopia. The latter is found in Dire Dawa at a distance of 510 km from Addis Ababa. They have been serving the ever-increasing population of the Harar town, Dire Dawa city, and their adjacent regions – Oromia and Somali. The ART clinic of the hospitals offers treatment service for new and follow-up HIV-infected individuals.<sup>18,19</sup>

### Study design and population

A hospital-based cross-sectional study was conducted among ART-naïve HIV-infected individuals at the ART clinic of the selected hospitals. Individuals aged <18 years and those who had taken antimicrobial treatment within 2 weeks before and during data collection were excluded from the study.

### Sample size and sampling technique

The sample size was determined using a single population proportion formula considering the prevalence of NTS bacteremia (12%) in HIV-infected patients,<sup>13</sup> 95% confidence level, and a 5% margin of error. Including a 10% nonresponse rate, the final sample size was 178. The hospitals were selected based on their HIV-infected patient load. Proportional allocation of the sample size was made for each selected hospital based on their size of ART-naïve HIV-infected individuals. Study participants were selected consecutively as they appeared at the ART clinic for their regular follow-up.

### Data and specimen collections

Data were collected from each participant by trained nurses using a pretested structured questionnaire at the time of visiting ART clinics of the selected hospitals. The questionnaire contains sociodemographic characteristics (sex, age, marital status, educational status, occupation, and income) and other related factors (hand washing practice, a habit of consuming raw food, and own domestic animals). The current level of CD4<sup>+</sup> counts of each participant was extracted from their medical record. After completion of an interview, 5–10 mL of blood was collected from each participant using a disposable sterile BD Vacutainer® blood collection tube. Each specimen was labeled with a unique code and transported to the Haramaya University College of Health and Medical Sciences Bacteriology Laboratory in a cold box for analysis.

### Nontyphoidal *Salmonella* identification

Bacterial culture isolation and identification were performed as described by Cheesbrough.<sup>20</sup> In brief, 5 mL of venous blood was inoculated into brain heart infusion broth (Oxoid, Ltd, Basingstoke, UK) and incubated at 35°C for 14 days. The bottles were inspected every day for visible signs of

bacterial growth such as turbidity above the red cell layer, colonies growing on top of the red cells, hemolysis, gas bubbles, and clots. Sample from the bottle with growth was Gram-stained and subcultured on *Salmonella-Shigella* agar, MacConkey agar, and xylose lysine deoxycholate agar for bacteria identification. Presumptive *Salmonella* colonies were further investigated biochemically using triple sugar iron agar, Christensen's urea medium, catalase, Voges-Proskauer, methylene red, Simmon's citrate agar, lysine iron agar, indole, oxidase, and motility tests. Serotyping of NTS isolates was performed by the slide agglutination method using commercial antisera (Denka Seiken, Tokyo, Japan) according to Kauffmann-White-Le Minor scheme.<sup>21</sup> All media were obtained from Oxoid, Basingstoke, England.

## Antimicrobial susceptibility test

Antimicrobial susceptibility testing was performed using the Kirby-Bauer disk diffusion method as described by the Clinical and Laboratory Standards Institute (CLSI).<sup>22</sup> The bacterial suspension was prepared by homogenizing three to five pure colonies of similar appearance in 4–5 mL sterile physiological saline (0.85% NaCl) until the suspension becomes equivalent to 0.5 McFarland turbidity standard. The standardized suspension was transferred using a sterile cotton swab and lawn evenly over the surface of Mueller-Hinton agar (Thermo Fisher Scientific Oxoid Ltd, Basingstoke, England) plates. Nine antimicrobials (Thermo Fisher Scientific Oxoid Ltd), which are commonly prescribed for the treatment of NTS bacteremia, including ampicillin (10 µg), chloramphenicol (30 µg), tetracycline (30 µg), ciprofloxacin (5 µg), ceftriaxone (30 µg), nalidixic acid (30 µg), gentamycin (10 µg), sulfamethoxazole-trimethoprim (23.75/1.25 µg), and kanamycin (30 µg), were placed onto the surface of the inoculated plates using automatic disk dispenser. The plates were incubated aerobically at 37°C for 18–24 hours. The diameter of the inhibition zone was measured to the nearest millimeters using a digital caliper and interpreted as sensitive (S), intermediate sensitive (I), or resistant (R) based on the CLSI criteria.<sup>22</sup>

## Quality control

A structured English questionnaire was translated into local languages (*Amharic*, *Afan Oromo*, and *Somali*) by language experts, and back to English by other language experts to assure its quality. The questionnaire was pretested on 5% of the sample size among ART-naïve HIV-positive patients in the Haramaya District Hospital, Eastern Ethiopia. Training was given to data collectors before the actual data collection. The

identification of NTS, serotyping, and antimicrobial susceptibility testing were performed by two microbiologists. Sterility and performance of each culture medium, and antimicrobial disks quality conditions were checked prior to the tests using the American Type Culture Collection (ATCC) reference strains such as *S. aureus* (ATCC® 25923), *Escherichia coli* (ATCC® 25922), *Streptococcus pneumoniae* (ATCC® 49619), *Salmonella typhimurium* (ATCC® 13311), and *Pseudomonas aeruginosa* (ATCC® 27853). The standardized operating procedures and manufacturer's instruction were strictly followed.

## Data analysis

Data were coded, cleaned, verified, and entered into the Epi-Info™ version 3.5.1 (CDC, Atlanta, GA, USA). The analysis of data was done using the Statistical Package for Social Sciences version 20.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to present the findings. Bivariate and multivariate logistic regression analyses were performed to assess the association between predictor variables and the outcome variable. Variables with a *P*-value <0.25 in the bivariate logistic regression model were considered in the multivariate logistic regression model for controlling potential confounding factors. Crude odds ratio (COR) and an adjusted odds ratio (AOR) were used to determine the significance of the outcome predictors. A *P*-value <0.05 was considered to indicate statistical significance.

## Ethical statement

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed and ethically approved by the Institutional Health Research Ethics Review Committee of the College of Health and Medical Sciences, Haramaya University. Official permission was secured from the management of Hiwot Fana Specialized University, Jugal, and Dilchora Hospitals before the commencement of the study. Data were collected after informed, voluntary, written, and signed consent obtained from each study participant. Information obtained during the study was kept confidential. The findings of infected individuals were communicated to attending clinician for appropriate treatment and management.

## Results

### Characteristics of the study participants

Out of the total (178), 170 ART-naïve HIV-infected adult individuals were enrolled in this study; making a response rate of 95.5%. Of which, 51.8% were females. The age of the study participants ranges from 18 to 66 years, with a mean ( $\pm$  standard deviation) age of 33.6( $\pm$ 8.3) years. Almost

half of the participants (52.4%) were found in the age range between 30 and 39 years. Of the total, a large proportion (42.4%) of participants were married, attended elementary school (42.9%), and earned an average monthly income between 35.85 and 53.76 USD (38.8%) (Table 1).

## Prevalence and associated factors

The overall prevalence of NTS bacteremia was 10% (17/170; 95% CI: 5.93–15.54). The majority of isolates were detected among participants who reported lack of a hand washing habit with soap after the use of the toilet (53.8%) followed by those who did not wash their hands before food preparation (41.7%), had a CD4<sup>+</sup> count <200 cells/μL (39.1%) and age >39 years (17.1%). A lack of hand washing habit with a soap before food preparation (AOR: 13.1, 95% CI: 10.40–15.30) and a CD4<sup>+</sup> count <200 cells/μL (AOR: 3.61, 95% CI: 1.74–5.25) were found to significantly increase the odds of having NTS bacteremia among ART-naïve HIV-infected adult individuals (Table 2).

**Table 1** Sociodemographic characteristics of ART-naïve HIV-infected adult individuals at three public hospitals in Eastern Ethiopia, 2017/8

Characteristics		Frequency	%
Sex	Male	82	48.2
	Female	88	51.8
Age (in years)	18–29	46	27.1
	30–39	89	52.4
	40–49	25	14.7
	>49	10	5.9
Marital status	Married	72	42.4
	Single	32	18.8
	Divorced	44	25.9
	Widowed	22	12.9
Educational status	Unable to read and write	33	19.4
	Read and write	5	2.9
	Elementary school (Grade 1–8)	73	42.9
	Secondary school (Grade 9–12)	47	27.7
	Certificate and above	12	7.1
Occupation	Government employee	11	6.5
	Private employee	46	27.1
	Farmer	6	3.5
	Daily labor	47	27.6
	Unemployed	7	4.1
	Housewife	20	11.8
	Student	4	2.4
	Others <sup>a</sup>	29	17.1
Average monthly income (in USD)	<17.92	18	10.6
	17.92–35.84	25	14.7
	35.85–53.76	66	38.8
	>53.76	61	35.9

**Note:** <sup>a</sup>Retired, merchant, housemaid, nongovernmental organization, and private job.  
**Abbreviation:** ART, antiretroviral therapy.

## Antimicrobial susceptibility pattern

Of the total NTS isolates (17), 76.5% showed sensitivity to gentamycin followed by ciprofloxacin (70.5%) and ceftriaxone (58.8%). Most isolates exhibited a high level of resistance to tetracycline (88.2%), chloramphenicol (76.5%), ampicillin (70.6%), and sulfamethoxazole–trimethoprim (70.6%). None of the isolates showed sensitivity or resistance to all antimicrobials in the testing panel (Table 3).

## Discussion

Nontyphoidal *Salmonella* bacteremia causes a significant public health problem and represents an important cause of morbidity and mortality in HIV-infected patients.<sup>3,23</sup> The prevalence of NTS bacteremia in this study was shown to be 10% (95% CI: 5.93–15.54). This finding suggests that the individuals remain at a higher risk for other coexistent life-threatening opportunistic infections and may present with the dual management considerations of comorbid conditions. A similar finding was reported in Ekiti State, Nigeria (12%),<sup>13</sup> Mwanza, Tanzania (7.6%),<sup>24</sup> and the National Taiwan University Hospital, Taiwan (6.7%).<sup>14</sup> But, it was higher than the findings reported from Dhaka, Bangladesh (0.2%)<sup>25</sup> and Baltimore, USA (0.2%).<sup>26</sup> A higher prevalence of NTS bacteremia in this study might be due to the exclusion of HIV-positive individuals who had exposure to antimicrobial treatment (inhibit the growth of bacteria) before sample collection and experienced ART, while included in the above comparative studies. The other reason for variation might be due to a difference in geographical location, sociodemographic status, and personal hygiene.

Factors such as hand washing habit, contact with pet animals, consumption of raw or improperly cooked meat, milk, and vegetables have been indicated as potential sources of *Salmonella* infection.<sup>27–29</sup> In the present study, a lack of hand washing habit before food preparation was found to increase the odds of acquiring NTS bacteremia (AOR:13.1, 95% CI: 10.40–15.30). This was inconsistent with the study conducted in Hawassa University Hospital, southern Ethiopia.<sup>30</sup> Health education regarding personal hygiene, hand washing before and after food preparation, surveillance of NTS infection, and isolation of identifying cases are possible solutions for prevention and control of NTS bacteria.<sup>11</sup>

Several immune defects have been contributed to the susceptibility of HIV-infected individuals to NTS bacteremia. These include the depletion of CD4<sup>+</sup>, loss of IL-17-producing CD4<sup>+</sup> T cells in the gut mucosa,<sup>7</sup> and dysregulated excess production of anti-lipopolysaccharide

**Table 2** Bivariate and multivariate analyses of NTS bacteremia among ART-naïve HIV-infected adult individuals at three public hospitals in Eastern Ethiopia, 2017/8

Characteristics		NTS bacteremia		COR (95% CI)	AOR (95% CI)
		Yes (%)	No (%)		
Sex	Male	8 (9.8)	74 (90.2)	0.94 (0.34–2.58)	0.68 (0.16–2.84)
	Female	9 (10.2)	79 (89.8)	I	I
Age (in years)	18–39	11 (8.1)	124 (91.9)	0.42 (0.14–1.25)	0.47 (0.10–2.21)
	>39	6 (17.1)	29 (82.9)	I	I
Average monthly income (in USD)	<53.76	9 (8.3)	100 (91.7)	0.59 (0.21–1.63)	0.70 (0.16–2.91)
	≥53.76	8 (13.1)	53 (86.9)	I	I
Educational status	Illiterate	6 (8)	27 (92)	0.45 (0.04–4.46)	0.32 (0.03–2.51)
	Literate	7 (5.1)	138 (94.9)	I	I
Marital status	Married	7 (9.7)	65 (90.3)	0.94 (0.34–2.62)	0.57 (0.11–2.83)
	Single, divorced, or widowed	10 (10.2)	88 (89.8)	I	I
Hand washing after the use of the toilet	No	7 (53.8)	6 (46.16)	2.01 (0.76–3.85)	1.14 (0.06–2.42)
	Yes	6 (10.5)	51 (89.5)	I	I
Hand washing before preparing food (n=148)	No	5 (41.7)	7 (58.3)	10.1 (2.66–38.10)	13.1 (10.40–15.30)*
	Yes	9 (6.6)	127 (93.4)	I	I
Consumption of raw or improperly cooked meat	No	8 (7.8)	94 (92.2)	0.55 (0.20–1.52)	1.34 (0.27–6.67)
	Yes	9 (13.2)	59 (86.8)	I	I
Consumption of raw milk and milk products	No	7 (6.4)	102 (93.6)	0.35 (0.12–0.97)	0.24 (0.05–1.13)
	Yes	10 (16.4)	51 (83.6)	I	I
Consumption of raw vegetables	No	6 (10.0)	54 (90.0)	1.00 (0.35–2.85)	0.67 (0.12–3.68)
	Yes	11 (10.0)	99 (90.0)	I	I
Consumption of raw or improperly cooked eggs	No	11 (8.2)	123 (91.8)	0.44 (0.15–1.30)	0.47 (0.08–2.84)
	Yes	6 (16.7)	30 (83.3)	I	I
Dog or cat ownership	No	12 (10.7)	100 (89.3)	1.27 (0.42–3.80)	0.85 (0.19–3.68)
	Yes	5 (8.6)	53 (91.4)	I	I
Current CD4 <sup>+</sup> count (cells/μL)	<200	9 (39.1)	14 (60.9)	11.1 (3.72–33.5)	3.61 (1.74–5.25)*
	≥200	8 (5.4)	139 (94.6)	I	I

Note: \*P<0.05.

Abbreviations: AOR, adjusted odds ratio; COR, crude odds ratio; NTS, nontyphoidal *Salmonella*.

**Table 3** Antimicrobial susceptibility pattern of NTS isolated from blood specimens of ART-naïve HIV-infected adult individuals at three hospitals in Eastern Ethiopia, 2017/2018

NTS isolates	Antimicrobial susceptibility, n (%)									
	Pattern	AMP	C	TE	CIP	CRO	NA	GN	SXT	K
n=17	S	5(29.4)	3(17.6)	2(11.8)	12(70.5)	10(58.8)	7(41.2)	13(76.5)	5(29.4)	4(23.5)
	I	0	1(5.9)	0	1(5.9)	0	2(11.8)	0	0	3(17.6)
	R	12(70.6)	13(76.5)	15(88.2)	4(23.5)	7(41.2)	8(47.0)	4(23.5)	12(70.6)	10(58.8)

Abbreviations: AMP, ampicillin; ART, antiretroviral therapy; C, chloramphenicol; CIP, ciprofloxacin; CRO, ceftriaxone; GN, gentamycin; I, intermediate; K, kanamycin; NA, nalidixic acid; NTS, nontyphoidal *Salmonella*; R, resistant; S, sensitive; SXT, sulfamethoxazole–trimethoprim; TE, tetracycline.

immunoglobulin G that inhibits serum killing of extracellular *Salmonella* in a concentration-dependent fashion.<sup>23,31</sup> In the present study, HIV-infected individuals who had a CD4<sup>+</sup> count <200 cells/μL was 3.6 times more likely found to be infected with NTS bacteria (AOR: 3.61, 95% CI: 1.74–5.25). This finding was in agreement with other studies conducted elsewhere,<sup>8,26,30</sup> suggesting unfavorable immunological and virological responses contributed to increased risk of NTS bacteremia.

Drugs, including tetracycline, chloramphenicol, ampicillin, and sulfamethoxazole–trimethoprim have long been used for the treatment of various diseases and opportunistic infections in Ethiopia.<sup>32</sup> Patients infected with resistant *Salmonella* may experience failure of empirical and prophylactic antimicrobial therapy.<sup>3</sup> The resistance shown in this study to sulfamethoxazole–trimethoprim (70.6%), which is used as a prophylactic for the prevention of opportunistic infection, including NTS bacteremia in HIV-infected individuals, is of particular con-



cern. Reduced efficacy of sulfamethoxazole–trimethoprim may prompt a physician to hospitalize a patient because symptoms persist or other medical complications arise. The resistance is likely to have developed due to prolonged use, unrestricted, frequent and inappropriate use of empiric treatment, and patients' own self-medication.<sup>33</sup> Hence, its use as a prophylaxis needs to be revised by the policymakers. The resistance of gentamycin, ciprofloxacin, and ceftriaxone was low in this study and can be the drug of choice for the treatment of NTS bacteremia in HIV-positive patients.

This study provides the largest description to date on NTS bacteremia in the eastern part of our country and highlights the similarities and differences of antimicrobial susceptibility profiles of isolates between similar study settings. However, since our study was health facilities-based, and focused mainly on ART-naïve HIV-infected adult individuals, the samples might have lacked representativeness and the findings might not be generalizable to all HIV-positive populations. The study also fails to demonstrate an association in several comparison variables due to the small sample size. Moreover, we did not perform molecular typing to identify the responsible gene conferring resistance due to the lack of laboratory facilities.

## Conclusion

In conclusion, the prevalence of NTS bacteremia was high. HIV-infected individuals who did not have a habit of washing hands before preparation of food and whose CD4<sup>+</sup> count was <200 cells/μL had higher odds of NTS bacteremia. Resistance to tetracycline, chloramphenicol, ampicillin, and sulfamethoxazole–trimethoprim was very common. Investment in improved culture identification of *Salmonella*, antimicrobial susceptibility testing, and surveillance systems is likely to be a highly cost-effective strategy. In settings where there are no laboratory facilities, gentamycin, ciprofloxacin, and ceftriaxone can be used for the treatment of the NTS bacteremia. Future studies need to focus on a longitudinal study by incorporating large population from health facilities and communities to assess the true prevalence of NTS as well as to test the efficacy of antimicrobial treatment in HIV-infected patients.

## Data sharing statement

The authors declare that all the necessary data are fully described within the manuscript.

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## Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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