Gender Differences in Rates of Carriage and Bloodstream Infection Caused by Methicillin-Resistant Staphylococcus aureus: Are They Real, Do They Matter and Why?

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There is increasing interest in sexual and gender dimorphism in disease. We reviewed the epidemiology of methicillin-resistant Staphylococcus aureus (MRSA) carriage and bloodstream infection (BSI), which shows a male predominance, and explored some of the possible reasons. Males are more prone to bacterial sepsis, but some studies suggest females may have a poorer prognosis from BSI. Hand-hygiene behavior varies according to gender. Males are less compliant, which in turn may predispose them to higher colonization and infection rates. Female hormones such as estrogen affect the expression of virulence factors in Pseudomonas aeruginosa, and although not studied, this may also apply to S. aureus. Further research is required on the relationship between gender and risk of infection, the reasons for higher MRSA carriage and BSI rates in males, the value of gender-specific infection prevention campaigns, and other factors such as the possible role of contact sports and occupation.

Keywords. MRSA; gender; behavior; hand hygiene; estrogen.

Staphylococcus aureus commonly colonizes the skin and mucosa and is an important cause of minor skin infections such as impetigo and serious infections such as bloodstream infections (BSI). While the incidence of methicillin-resistant S. aureus (MRSA) has recently declined in many countries, it remains an important cause of infection. Risk factors for MRSA include previous hospitalization, major surgery, exposure to antibiotics, significant underlying chronic diseases, and, in some studies, male gender. Knowledge of these risk factors helps identify patients most likely to become colonized or infected and assists in developing multimodal prevention strategies, including active screening. Given the increasing research emphasis on sexual and gender dimorphism of disease [1], it is timely to explore some of the possible underlying biological mechanisms and behavioral patterns for sex differences in MRSA, including different colonization and infection rates and outcomes.

We reviewed the patterns of colonization, infection, and outcome with MRSA according to gender and explored behavioral factors that might account for this. The scientific literature in English on MRSA through December 2014 in PubMed was reviewed. Search terms used in addition to MRSA included screening, carriage, colonization, gender terms such as male and female and sex factors, BSI, bacteremia, invasive infection, risk factors, behavioral factors, hygiene terms such as hand washing and hygiene, personal behavior, physiology, and hormonal influences, individually as well as in combination. In areas where the literature was lacking or nonexistent for MRSA, we compared known gender differences for other microbial infections. The references in papers obtained were also reviewed to determine if there were other relevant studies not identified in the original literature search. Many studies
address colonization and infection caused by methicillin-susceptible *S. aureus* (MSSA) as well as MRSA. Where this occurred, we focused on aspects of MRSA.

**CARRIAGE**

Wertheim and colleagues reviewed the role of nasal carriage in *S. aureus* infections and how it predisposes to subsequent infection [2]. Among the host factors for colonization, they identified age, sex, and ethnicity and suggested that the large number of apocrine sweat glands in the nose may be important determinants in *S. aureus* nasal carriage. The nose is the most commonly colonized site, and approximately 27% of the general population are *S. aureus* carriers [2].

A cross-sectional study of more than 32 000 nonhospitalized patients aged >4 years, recruited by family doctors in 9 European countries, reported an *S. aureus* carriage rate of 21.6% [3]. Carriage of *S. aureus* was most frequent in Sweden (29.4%), but the highest MRSA prevalence was 2.1% in Belgium [3]. Overall, males were more likely than females to be carriers, with an odds ratio (OR) of 1.38 (1.31–1.46). However, the authors did not specify whether this gender difference also applied to MRSA. In a Swiss study, where admissions to an acute care hospital were screened for MRSA, 399/12 072 (3.3%) admissions were positive for MRSA [4]. Nine independent risk factors were found, including male sex with an OR of 1.9 on multivariate analysis. Another study of 23 314 patients screened on hospital admission to a US hospital found that 520 (2.2%) patients were MRSA positive and that male gender was a significant risk on multivariate analysis, with an OR of 1.3 (1.1–1.6) [5].

In other studies, a higher prevalence of MRSA was documented among males, but the findings were not statistically significant. For example, a recent survey of 590 US facilities that included 67 412 in-patients detected 4476 (6.6%) MRSA-positive patients of which 52.2% were male. However, this was not reported as being statistically significant [6].

**BLOODSTREAM INFECTIONS**

When considering invasive MRSA infection, much of the scientific literature focuses on BSI as there is an agreed definition, that is, the presence of *S. aureus* in blood with appropriate symptoms, its clinical significance is well recognized, and because much of the data are captured as part of large regional, national, or international surveillance systems. Furthermore, the data on other invasive infections such as osteomyelitis or meningitis are much less extensive or are inconsistent in the reporting of risk factors. Also, some BSI studies are single hospital population–based reports and may be too small to demonstrate statistical significance. We therefore focused on larger studies. Although many of these studies included data on MSSA BSI, we focused on aspects of MRSA.

A population-based surveillance study of data collected regionally in Australia, Sweden, and Denmark assessed 83 million person-years of BSI surveillance data (Table 1) [7]. The overall annual infection rate for *S. aureus* BSI was 26.1/100 000 and specifically for MRSA was 1.9/100 000. Compared with females, males were at increased risk overall for MSSA and MRSA BSI, that is, the relative risks were 1.63 and 1.72, respectively [7]. Data from 5 independent, prospective cohort studies in 20 centers in Germany, Spain, the United Kingdom, and the United States between 2006 and 2011 found that males were statistically overrepresented in the 5 studies, accounting for 54.7%–66.6% of patients [8].

The incidence of community- and hospital-onset MRSA BSI in England and the United States between 2006 and 2007 was compared [9]. While the 2 surveillance systems are not identical, there were nonetheless some interesting comparisons. The rate of MRSA BSI was higher in the United States than in England, 29.3 vs 11.2/1 000 000 population, and rates were higher in men compared with women, 1.5- and 1.8-fold higher in the United States and England, respectively [9]. A study from Calgary, Canada, between 2000 and 2006 found that the incidence of *S. aureus* BSI was 19.7/100 000 person-years and that both infections caused by MSSA and MRSA increased with age [10]. Overall, 62% of episodes occurred in males; for MSSA BSI, the risk among males compared with females was 1.68-fold higher and for MRSA it was 1.39-fold higher [10].

Kallen and colleagues reported the results of an active population-based surveillance study of invasive MRSA in 9 centers representing 8 states in the United States and covering a population of approximately 15 million from 2005 to 2008 [11]. This study included BSI and other infections such as bone and joint infections and categorized infections as hospital-onset, health-care-associated community-onset, and community-associated. Rates of MRSA infection in males were higher than for females, and there was an overall decrease in infections over the study period [11].

Mortality data from MRSA BSI suggest there may be some gender differences. In the data from 5 studies described above where males were overrepresented, male gender was not associated with mortality [8]. A prospective study of MRSA BSI in 21 Spanish hospitals from 2008 to 2009 followed up patients for mortality at 30 days after the first set of blood cultures [12, 13]. The median delay in starting appropriate antibiotic therapy was 1.8 days and the overall mortality was 32%. Age, especially >70 years, was the most consistent predictor of mortality; the mortality among females was 36% [12]. A study from England of 10 408 reports of MRSA BSI in 2004–2005 found that the risk of death within the first 7 days of diagnosis was statistically greater in females than in males, that is, 22% vs 19%. Also,
7-day case fatality rates were higher in women than men in every age group [14]. However, this study reported all-cause and not attributable or disease-specific mortality.

Many studies of BSI therefore show a male predominance for both MRSA and MSSA that may reflect higher infection rates for males. Furthermore, some studies suggest the possibility of a poorer outcome for female patients. The reasons for this are probably multifactorial, but behavioral and physiological factors may partly explain this difference.

**BEHAVIOR**

A number of hospital-based studies have described an association between healthcare staff hand-hygiene practice and MRSA colonization and infection rates [15]. This association has also been reported outside the healthcare setting [16]. Gender differences in behavioral practices among healthcare staff, such as for hand hygiene, may potentially influence MRSA colonization and infection rates.

Women have consistently been reported to clean their hands more frequently than men in a variety of settings (Table 2). In New Zealand and US public restroom observational studies, males had a significantly lower frequency of hand hygiene, soap use, and hand-hygiene duration [17, 18]. This has led some authors to propose gender-specific campaigns to improve hand-hygiene behavior [19]. When the theory of planned behavior was used to implement a hand-washing campaign among college students, females had more positive attitudes toward hand hygiene [20]. The influence of gender and hand-hygiene motivation was also explored in a study in motorway service station restrooms, where a series of messages encouraging hand hygiene were displayed [21]. Men responded better to disgust-based messages and women to messages based on activating preexisting knowledge about the dangers of failing to wash their hands [21].

Reports of healthcare staff hand-hygiene practice have also found a higher compliance in females in both healthcare and community settings, including among physicians [22–24].

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**Table 1. International, National, and Large Regional Studies on Staphylococcus aureus Bloodstream Infection, Including Methicillin-Resistant S. aureus, That Address Differences in Rates and Outcome According to Gender**

<table>
<thead>
<tr>
<th>Location and Year</th>
<th>Study Design</th>
<th>Main Findings</th>
<th>Comments</th>
<th>References</th>
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<tbody>
<tr>
<td>Finland, Australia, Canada, Denmark, and Sweden, 2000–2008</td>
<td>Population-based cohort of 18,430 episodes of S. aureus BSI</td>
<td>Male-to-female ratios for MSSA BSI and MRSA BSI were 1.63 and 1.72, respectively; CO-MSSA BSI stable, but HO-MRSA and MRSA BSI varied</td>
<td>Not stratified for risk factors; highlights regional differences</td>
<td>[7]</td>
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<td>Germany, Spain, United Kingdom, and the United States, 2006–2010</td>
<td>Five independent, prospective cohort studies of S. aureus BSI in 20 centers; 3544 cases of S. aureus BSI</td>
<td>21% due to MRSA; proportion of males with S. aureus BSI varied from 54.7% to 66.6%</td>
<td>Patients were from tertiary care centers; did not specify if CO- or HO-MRSA</td>
<td>[8]</td>
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<td>United Kingdom and the United States, 2006–2007</td>
<td>Compared data from mandatory surveillance of MRSA BSI (United Kingdom) with 11,431 cases, and population-based surveillance (United States) with 9324 cases</td>
<td>Male gender rates were 1.5 and 1.8 times higher in the United States and the United Kingdom, respectively; CO-MRSA 6.3-fold higher in the United States vs the United Kingdom, but HO-MRSA rates similar</td>
<td>No external validation in the United Kingdom; selected counties of 9 states in the United States may not be representative</td>
<td>[9]</td>
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<tr>
<td>Calgary, Canada, 2000–2006</td>
<td>Population-based surveillance of S. aureus BSI; 1441 cases</td>
<td>62% of cases in males; male-to-female ratio for MRSA BSI was 1.68 and 1.39 for MSSA BSI; CO-MSSA decreased over the study period</td>
<td>Not stratified for risk factors; data confined to 1 Canadian province</td>
<td>[10]</td>
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<tr>
<td>Spain, 2005</td>
<td>Prospective surveillance and collection of data in 21 centers; 579 episodes of MRSA BSI</td>
<td>Males accounted for 66% of cases; overall mortality, 36% in females; CO-MRSA accounted for only 4% of cases</td>
<td>Mainly focused on initial treatment and vancomycin minimum inhibitory concentrations</td>
<td>[12, 13]</td>
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<tr>
<td>England, 2004–2005</td>
<td>Population-based study to assess mortality in 10,408 cases of MRSA BSI</td>
<td>Mortality 1.16 times more common in females within 7 d; 22% in females and 19% in males</td>
<td>Not stratified for risk factors; used all-cause and not cause-specific mortality rates; cases not categorized as CO- or HO-MRSA</td>
<td>[14]</td>
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Abbreviations: BSI, bloodstream infection; CO, community onset; HO, hospital onset; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-susceptible S. aureus.
These differences also occur when staff are outside the healthcare setting, with increased rates of hand hygiene noted among female neurologists attending a conference, when compared with their male counterparts [24]. Gender differences in other personal hygiene issues may also potentially influence MRSA colonization and infection rates. Among Dutch patients attending a hospital outpatient department, nose pickers were significantly more likely to carry S. aureus. There was a positive correlation between the self-reported frequency of nose picking and the frequency of both positive culture results for S. aureus and the number of bacteria detected [25]. Self-reported nose picking and nail biting are higher in male college students [26]. However, whether this translates into gender differences throughout the general population and if it relates to differences in MRSA colonization and infection rates have not been reported.

Profession or occupation may also influence the likelihood of MRSA colonization and gender differences. In the livestock industry, MRSA colonization rates are higher than that of the general population, and within this industry they are higher in males than in females [27]. At an international conference for pig health, delegates, who were predominantly veterinarians, were screened for MRSA; 27/193 (13.9%) males and 4/69 females (5.7%) were colonized [28]. A Dutch study of veal calf farmers and their families that showed an association between animal exposure and human MRSA carriage also found that males were more often MRSA colonized than females (OR = 3.0) [29]. However, these differences may reflect more prolonged contact between males compared with females and animals among these occupational groups.

Gender differences and other activities such as playing contact sports may also play a role. Community-onset MRSA colonization and infection rates have not been reported.

Table 2. Recent Key Studies on Hand Hygiene and Gender Differences

<table>
<thead>
<tr>
<th>Location</th>
<th>Setting/Population</th>
<th>Study Design</th>
<th>Main Findings</th>
<th>References</th>
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<tbody>
<tr>
<td>New Zealand</td>
<td>Shopping mall public washrooms in 4 cities, 2006, general public</td>
<td>Direct observation of 1200 people by staff of local public health services or local authorities</td>
<td>Males (81.0%) had lower hand-hygiene compliance than females (92%); soap was used less frequently by males (66.2%) than females (76.5%)</td>
<td>[17]</td>
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<td>United States</td>
<td>University campus public restrooms, 2003, college students</td>
<td>Direct observation of 95 women and 80 men over 1 week; observer disguised their observations, which were made before and after placement of hand-hygiene promotional signs</td>
<td>Males washed their hands for shorter periods; 61% of women and 37% of men performed hand hygiene in the absence of a sign; this rose to 97% for women and fell to 35% of men when the sign was introduced</td>
<td>[18]</td>
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<tr>
<td>United States</td>
<td>Texas university restrooms, 2006, college students</td>
<td>Direct observation of 1400 hand-hygiene observations over 3 weeks; 700 observations made in the presence of a visual prompt; majority of observations made in female students (86%)</td>
<td>Hand hygiene and hand washing were higher in females, 59% vs 32% and 76% vs 57%, respectively, P &lt; .001; visual prompts made no difference according to gender</td>
<td>[19]</td>
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<tr>
<td>United States</td>
<td>University college restrooms, 2008–2010, college students</td>
<td>One-month poster campaign with 3 10-hour observation sessions of 1005 students by concealed observers; online survey of 188 students</td>
<td>Females had higher hand washing compliance, P &lt; .001, and soap use, P &lt; .001; females demonstrated more positive attitudes toward hand washing, greater behavioral intention, higher social expectations regarding hand washing, and higher rates of self-reported hand washing</td>
<td>[20]</td>
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<td>England</td>
<td>Highway service station toilets, 2008, general public</td>
<td>Data collected over 32 d on 108 000 males and 90 000 females; wireless devices unobtrusively observed soap use; text messages used to encourage hand washing displayed</td>
<td>Men responded better to disgust-based messages, increasing soap use by 9.8%, P = .001; women responded better to messages based on knowledge about the dangers of failing to wash hands, increasing soap use by 9.4%, P &lt; .001</td>
<td>[21]</td>
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<tr>
<td>Israel</td>
<td>Community teaching hospital, 2008, healthcare staff</td>
<td>Direct observation of 1035 hand-hygiene opportunities of 300 healthcare staff</td>
<td>Females complied with hand washing more than males, 80% vs 69%, P &lt; .0001</td>
<td>[22]</td>
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<tr>
<td>Australia</td>
<td>Critical care unit, 2001, healthcare staff</td>
<td>Covert observation of 249 hand-washing opportunities over a 3-month period</td>
<td>Females washed their hands significantly more often than males after patient contact, P = .0001; intergender differences reported for doctors, P = .0468, and ward staff, P = .0001</td>
<td>[23]</td>
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<tr>
<td>Austria</td>
<td>Conference center restrooms, 2013, conference delegates</td>
<td>Direct observation of hand hygiene of 200 neurologists over 6 days; hand hygiene defined as using soap and water</td>
<td>Female neurologists performed proper hand hygiene more often than their male counterparts, 87% vs 61%, P &lt; .001</td>
<td>[24]</td>
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</table>
(CO-MRSA) has been linked to contact sports. However, it is not clear whether this is because MRSA prevalence is more common in males or because males are more likely to participate in contact sports. CO-MRSA was responsible for 7 of 24 infectious diseases outbreaks in competitive sports between 2005 and 2010 [30]. Of these, 4 involved American football. In a risk factor prevalence study of children, MRSA was detected in 2.4% of children and MSSA in 24% and, while male gender was not associated with MRSA or MSSA, sports participation was borderline significant (P = .057) for MSSA colonization but not for MRSA colonization [31]. In a smaller study of 400 emergency department patients, 11 (3%) were MRSA positive in the nose and 16 (4%) at an extra nasal site. Among the significant risk factors for MRSA was playing contact sports. Although 60% of the patients with MRSA were male, male gender per se was not statistically significant as a risk factor [32]. While contact sports are associated with colonization and skin infections due to S. aureus, the interaction with gender is likely to be influenced by many factors including the population studied, the nature of the contact sports, and the participation in contact sports according to gender.

**PHYSIOLOGICAL AND IMMUNOLOGICAL FACTORS**

Sex differences are a known contributory factor in the susceptibility to infection [33]. However, the sex (genetic and physiological factors) and gender (population, behavior, and environmental influences) can complicate clinical trials and large-scale epidemiological studies with compounding and opposing impacts. Moreover, different bacterial species may elicit opposite responses among the sexes. For example, *Campylobacter* infection is more common in males, and this could be attributed to nutritional, behavioral, and environmental factors. However, bacterial virulence was higher in male mice compared with female mice in which these nonmicrobial factors were minimized, pointing to physiological and hormonal influences [34].

Hospital-acquired MRSA infections have been observed in all age spectra, although the rate of infection was highest among patients aged >65 years in one study, with a higher incidence among males [35]. These observations may rule out the premenopausal protective effects of estrogen in females, although immune responses appear to play a role in gender differences and fatal sepsis.

Males usually generate a more aggressive inflammatory immune response to microbial stimuli with a higher mortality rate, whereas females mount more protective immune and humoral responses. Clinical trials have shown that males are more prone to lethal bacterial sepsis than females, with a 70% mortality rate compared with 26% in female patients [36]. The poorer prognosis for males has been attributed to a higher level of the circulating inflammatory cytokine tumor necrosis factor-α, while females also had higher levels of the immunosuppressive cytokine interleukin (IL)-10. Thus, females may be protected from lethal sepsis by lowering the conditions for endotoxic shock through a reduction in inflammatory mediators and the suppression of the inflammatory immune response.

There is increasing evidence for marked sexual dimorphism in immune responses to infection. Although there is a paucity of data on the influence of estrogen in *S. aureus* infection, observations from cholera and *Escherichia coli*–induced infections in the gut clearly show hormonal protective effects in the female. Sexual dimorphism has been seen in animal models of toxin-induced secretory diarrhea. Estrogen is protective in shutting down secretion in intestinal cells exposed to cholera toxin or heat-stable *E. coli* [37]. Estrogen also confers resistance to streptococcal and other microbial infections, and resistance to some bacterial infections in the female can be reversed by testosterone treatment [38]. While there are few studies on microbial virulence during the menstrual cycle and none specifically for MRSA, there is strong evidence that postmenopausal women with undetectable plasma estrogen have a reduced adaptive immune response [39].

It is important to note that sexual dimorphism does not favor females for all microbial infections. The most detailed studies of gender differences in bacterial infections have been carried out in patients with cystic fibrosis (CF). Staphylococcal respiratory infections are more prevalent in prepubertal children with CF and decline with age to be replaced by *Pseudomonas aeruginosa*. CF gender studies have focused more on the latter bacterial infection, which occurs with high prevalence in high-estrogen states. In CF lung infections, for example, there is a clear gender difference where females are colonized earlier with *P. aeruginosa* and also develop more serious infections with *Burkholderia* spp. [40, 41].

The molecular mechanisms of estrogen-induced bacterial virulence in the CF airways and its gender dependency have been determined for *P. aeruginosa*, and comparative studies are now required for other opportunistic infections including *S. aureus* in the weakened lung of individuals with CF. There is a dearth of studies linking immunology, physiology, MRSA, and BSI. Hence we have extrapolated from the links between CF, pseudomonas infection, and gender.

Females with CF have shorter life expectancies than males (on average 9 years less), more serious infections, and poorer lung function [41]. The etiology of this gender difference is unclear, although sex differences appear just after puberty and suggest a role for reproductive hormones in exacerbating the disease in females with CF. Moreover, lung function varies throughout the menstrual cycle, with more frequent lung exacerbations during menstruation and subsequent improvement in the luteal phase [42]. Furthermore, lung exacerbations can be
directly correlated with plasma estrogen levels during the menstrual cycle [43]. Estrogen also inhibited Toll-like receptor-induced IL-8 release via estrogen receptor-beta–mediated activation of the secretory leucoprotease inhibitor and the sequestration of nuclear factor kappa B [44]. Furthermore, microbial mucoidy and alginate production are enhanced with high levels of estrogen [42]. These observations point to a determinant impact of estrogen in the CF “gender gap.”

It is interesting to note that even in normal non-CF bronchial epithelium, estrogen causes a reduced airway surface liquid layer to favor a decreased mucociliary clearance, mucus stagnation, and bacterial infection. Thus it is possible that even in normal airways, high estrogen states in females may predispose them to airborne MRSA bacterial infections due to compromised mucociliary clearance.

CONCLUSIONS

Larger studies strongly suggest that males have a higher risk of MRSA carriage and BSI; however, in some studies, females showed a poorer outcome from MRSA BSI. Males comply poorly with hand-hygiene recommendations compared with females, and gender differences in motivation for improvement have been reported. Future research focusing on why this is the case to inform gender-specific hand-hygiene improvement programs is needed. Other issues that might be relevant include occupation and participation in contact sports. A gender gap exists in susceptibility to some microbes and in the adaptive immune response, which has in part a physiological basis in reproductive hormone modulation of immune defense, bacterial virulence, and cell physiology. Further research linking gender dimorphism and higher MRSA carriage and BSI rates in males is required, such as the prospective evaluation of at-risk populations for colonization and infection. Female hormones such as estrogen affect the expression of virulence factors in P. aeruginosa in female patients with CF who have a poorer prognosis than males. Future studies should determine if this applies to other bacteria and other settings such as MRSA BSI.

Notes

Acknowledgments. We thank Breffni Smith and Gethin White for assistance with the literature searches.

Potential conflicts of interest. H. H. has received research support from Pfizer (Ireland) in recent years. He has also received lecture and other fees from Cepheid, Novartis, Astellas, and AstraZeneca. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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