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MAJOR ARTICLE

# Rate of Transmission of Extended-Spectrum Beta-Lactamase–Producing Enterobacteriaceae Without Contact Isolation

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**(See the Editorial Commentary by Kluytmans-van den Bergh and Kluytmans, on pages 1512–4.)**

***Background.*** Extended-spectrum beta-lactamase (ESBL)–producing Enterobacteriaceae are emerging worldwide. Contact isolation is recommended; however, little is known about the rate of transmission without contact isolation in the non-epidemic setting. Therefore, we aimed to estimate the rate of spread ($R_0$) of ESBL-producing Enterobacteriaceae in a tertiary care center with 5 intensive care units.

***Methods.*** In this observational cohort study performed from June 1999 through April 2011, all patients at the University Hospital Basel, Switzerland, who were hospitalized in the same room as a patient colonized or infected with an ESBL-producing Enterobacteriaceae for at least 24 hours (index case) were screened for ESBL carriage by testing of rectal swab samples, swab samples from open wounds or drainages, and urine samples from patients with foley catheters. Strains with phenotypic evidence for ESBL were confirmed by polymerase chain reaction. Nosocomial transmission was assumed when the result of screening for ESBL carriage in a contact patient was positive and molecular typing by pulsed-field gel electrophoresis (PFGE) revealed clonal relatedness with the strain from the index patient.

***Results.*** Active screening for ESBL carriage could be performed in 133 consecutive contact patients. Transmission confirmed by PFGE occurred in 2 (1.5%) of 133 contact patients, after a mean exposure to the index case of 4.3 days.

***Conclusions.*** The estimated rate of spread of ESBL-producing Enterobacteriaceae—in particular, *Escherichia coli*—was low in a tertiary care university-affiliated hospital with high levels of standard hygiene precautions. The low level of nosocomial transmission and the rapid emergence of community-acquired ESBL challenge the routine use of contact isolation in a non-epidemic setting, saving resources and potentially improving patient care.

Multidrug-resistant organisms, including extended-spectrum beta-lactamase (ESBL)–producing Enterobacteriaceae, are rapidly emerging worldwide [1]. This trend is of particular concern, because gram-negative bacteria account for a large proportion of health care–associated infections, especially in intensive care units [1, 2]. Infections caused by ESBL-producing organisms have been associated with longer hospital stay, reduced rates of clinical and microbiological response, and poor outcome [3, 4]. The Centers for Disease Control and Prevention (CDC) has classified ESBL-producing pathogens as multidrug-resistant organisms (MDRO) and has declared the prevention and control of MDROs to be a national priority [5]. Therefore, the CDC has published recommendations to guide the implementation of strategies and practices to prevent the transmission of such organisms in health care settings [5]. Among recommendations concerning judicious use of antibiotics, administrative measures, surveillance, and education of health care personnel, contact precautions are recommended in acute care hospitals for patients colonized or infected with target MDROs, as judged by local recommendations to be of

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epidemiologic significance [5, 6]. In Switzerland, national guidelines recommend contact precautions for all patients colonized or infected with ESBL-producing organisms in acute care facilities [7]. At the University Hospital Basel, Switzerland, therefore, all patients with detection of ESBL-producing pathogens are assigned to contact precautions, including the universal use of gowns and gloves and placement in single rooms. Active surveillance by screening for ESBL carriage is performed for all patients who were hospitalized in the same room for >24 hours with a patient colonized or infected with an ESBL-producing pathogen before the positive ESBL result was reported and the patient was assigned to contact precautions. The CDC recommendation is not based on large clinical trials evaluating the effect of contact isolation compared with non-contact isolation. However, knowledge on the rate of spread is essential to guide future recommendations on contact precautions to reduce transmission of ESBL-producing Enterobacteriaceae.

The aim of this study was therefore to estimate the rate of spread ($R_0$) for ESBL-producing Enterobacteriaceae in a tertiary care center with 5 intensive care units over an 11-year study period.

## METHODS

### Setting

The University Hospital Basel is a tertiary care center with 5 intensive care units in Basel, Switzerland, with 855 beds, that admits >30 000 adult patients per year. The study was approved by the local ethics committee as part of the quality assurance program, and informed consent was waved.

### Study Design

This is an observational cohort study.

### Data Collection

Data were collected from June 1999 through April 2011. The following baseline characteristics and clinical features of index and contact patients were assessed: age, sex, length of hospital stay (days), length of ICU stay (hours), the number of underlying diseases, the number of previous hospital stays (before detection of an ESBL-producing pathogen for index patients and before screening for ESBL-carriage for contact patients), leukocyte count, C-reactive protein and albumin levels on the day of detection of an ESBL-producing pathogen for index patients and on the day of screening for ESBL-carriage for contact patients (± 7 days), and outcome (defined as discharge home, transfer to another hospital, or death).

### Definition of Index Patients

All patients colonized or infected with an ESBL-producing pathogen in any specimen from each body site were assigned to contact precautions exclusively in single rooms. Patients from whom an ESBL-producing pathogen was isolated were marked in our electronic chart. An e-mail alarm was set for infection control staff, after the patient was scheduled for an in- or outpatient visit or when admitted as emergency. In addition, the requirement of contact isolation was listed on the top page of the administrative and medical charts.

Contact precautions were discontinued when a patient had 3 negative results, defined as no ESBL detection from each of the following body sites: the site in which ESBL-producing pathogens were first detected, the rectum, urine, and any open wounds or drainages [8].

### Definition of Contact Patients

All patients hospitalized in the same room as an index patient colonized or infected with ESBL-producing Enterobacteriaceae for at least 24 hours were defined as contact patients.

### Contact Time

Contact time of an index patient with a contact patient was defined as the period that the 2 shared the same room together without initiation of contact precautions for the index patient before colonization or infection with an ESBL-producing pathogen was identified by the microbiology laboratory.

### Definition of Transmission

Transmission was regarded to have occurred when the result of screening for ESBL carriage of a contact patient was positive and the polymerase chain reaction (PCR) subtype and molecular typing by pulsed-field gel electrophoresis (PFGE) revealed identity with the strain of the index patient.

### Active Surveillance for ESBL Carriage

Screening for ESBL carriage was performed by testing of rectal swab samples and swab samples from any open wounds or drainages and culture of urine samples from patients with foley catheters. Active surveillance was performed for all contact patients, as defined above, as long as they were still hospitalized and were not receiving antibiotic treatment active against ESBL-producing pathogens, as determined by the susceptibility testing of the isolate of the respective index patient, to avoid false screening results.

In addition, all patients with known ESBL carriage were screened when they were readmitted to the hospital.

### Standard Precautions

Standard precautions include the proper use of hand hygiene (as indicated in the World Health Organization and CDC guidelines) [6, 9] and the use of personal protective equipment (ie, gloves, gowns, masks, and eye protection) for procedures involving contact with body fluids, as outlined by the CDC guidelines [6].

### Contact Precautions

Contact precautions involved assignment to a single room and use of gloves and gowns by both health care workers and visitors at entrance [6].

### ESBL Identification

For microbiological detection of ESBL, standard culture methods were performed in accordance with the guidelines of the Clinical and Laboratory Standards Institute (formerly National Committee for Clinical Laboratory Standards) [10]. Routine susceptibility testing was performed using microbroth dilution (Micronaut-S, Merlin) with use of the following compounds for ESBL screening: cefpodoxime, ceftriaxone, ceftazidime, and aztreonam. If the screening test yielded any positive result, confirmation testing was performed using Etest strips (AB Biodisk[now, bioMérieux]) containing cefotaxime or ceftazidime, each tested with and without clavulanic acid.

### Genotypic Identification of ESBL

Total DNA was extracted from approximately $3 \times 10^7$ colony-forming units of bacterial cells with use of 200 mL InstaGene Matrix (BioRad), according to the manufacturer's instructions. The complete open reading frame of genes encoding sulfhydryl variable (SHV) β-lactamases was amplified with the primer pairs SHV-UF (5′-GCCGGGTTATTCTTATTTGT CGC-3′) and SHV-LR1 (5′-TCACCACCATCATTACCGAC-3′). For detection of *bla*CTX-M and identification of CTX-M-cluster, 2 different methods were applied [11]. In the first assay, a 512-bp internal fragment ranging from position 213 to position 724 ($bla_{\text{CTX-M-1}}$) was amplified using the degenerative oligonucleotides CTX-F2 (5′-GTGCAGYACCAGTAARGTKATGG-3′) and CTX-M-R1 (5′-CDMCGCT GCCGGTYTTATC-3′). The CTX-M–positive isolates obtained during 2006 and 2007 were subjected to a multiplex PCR, as described elsewhere [12]. Sequencing of amplicons was performed using an ABI 3130 Genetic Analyzer (Applied Biosystems).

### Molecular Typing

Molecular typing was performed using PFGE [13], to examine the identity of the strains. DNA restriction fragments were separated by PFGE after *Xba*I digestion and dendrograms were drawn with use of the software GelCompar, version 4.5 (Applied Maths).

### Statistical Analyses

Data were entered into a database (Excel; Microsoft) and then imported into SPSS (version 120.0; SPSS). Univariate analysis was performed using the $\chi^2$ test or Fisher's exact test, where appropriate, for categorical variables and 2-tailed Student's *t* test for continuous variables.

## RESULTS

From June 1999 through April 2011, 324 patients infected or colonized with ESBL-producing Enterobacteriaceae accounted for 551 hospital admissions. A total of 93 (28.7%) of 324 were index patients and had a total of 220 contact patients. The median number of contacts for each index patient was 1.0 (range, 1–7 contacts). Active screening for ESBL carriage could be performed in 133 (60%) of 220 consecutive contact patients. Screening could not be performed for the remaining 87 contact patients, either because they were already discharged from the hospital at the time that the result was obtained for their respective index patient or because they were receiving antibiotic treatment active against the ESBL-producing pathogen for which screening was intended.

There were no significant differences in age and sex between index and contact patients (Table 1). However, length of hospital stay, number of previous hospital stays, the number of underlying diseases, and mean albumin level at admission differed significantly between the 2 groups (Table 1).

*Escherichia coli* was the most common ESBL-producing pathogen detected in index patients (68 [73.1%] of 93), followed *by Klebsiella pneumoniae* (22 [23.7%] of 93) and *Klebsiella oxytoca*, *Citrobacter freundii,* and *Enterobacter aerogenes* (1 case each). Sixty (65%) of 93 ESBL isolates were molecularly characterized. The CTX-M genotype was most commonly identified (47 [50.5%]), followed by SHV (9 [9.7%]) and others (4 [4.3%]).

A total of 579 contact days was recorded during the study period, with a mean of 4.3 ±4.89 days and a median of 3 days (range, 1–37 days). Screening results revealed carriage of ESBL-producing Enterobacteriaceae in 7 (5.3%) of the 133 examined contact patients. In 6 and 1 contact patients, ESBL-producing *E. coli* and *K. pneumoniae,* respectively, were detected, representing the same species from both index and contact patient. Although in 6 of these 7 pairs of index and contact patients, the same molecular ESBL type was found (Table 2), PFGE only revealed identity of the strains in 2 (30%) of 7 contact patients (Figures 1 and 2). Therefore, transmission as demonstrated by PFGE had been definitely confirmed in only 2 (1.5%) of 133 contact patients.

The first transmission occurred on a surgical ward in a 2-bed room after 10 days of contact with the index patient. The 2 patients staying in the same room shared the same bathroom. ESBL-producing *E. coli* was detected by rectal swab of the contact patient and was interpreted as colonization, because no clinical signs of infection could be detected. The second transmission occurred in a general medical ward, also in a 2-bed room, after 9 days of contact; the 2 patients again shared the same bathroom. ESBL-producing *K. pneumoniae* was detected by rectal swab and was regarded as colonization. Therefore, exposure to an ESBL-positive index patient did not

**Table 1. Baseline Characteristics of Index Patients Colonized or Infected With Extended-Spectrum Beta-Lactamase–Producing Pathogens and Contact Patients**

| Characteristic | Index Patients (n = 93) | | Contact Patients (n = 133) | | *P* | OR | 95% CI |
|---|---|---|---|---|---|---|---|
| Age (years) | | | | | | | |
| Mean (± SD) | 67.05 | (±17.35) | 70.43 | (±17.37) | .152 | | |
| Sex | | | | | | | |
| Male | 42 | 45.2% | 64 | 48.1% | .661 | 0.888 | .522–1.511 |
| Female | 51 | 54.8% | 69 | 51.9% | | | |
| Length of hospital stay (days) | | | | | | | |
| Mean (± SD) | 29.55 | (±25.51) | 21.25 | (±20.84) | .008 | | |
| Median (range) | 22.00 | (2–127) | 14 | (2–130) | | | |
| Length of ICU stay (hours) | | | | | | | |
| Mean (± SD) | 13.09 | (±77.64) | 28.8 | (±124.24) | .284 | | |
| Number of underlying diseases | | | | | | | |
| Mean (± SD) | 10.08 | (± 4.95) | 7.35 | (±4.58) | <.001 | | |
| Number of previous hospital stays | | | | | | | |
| Mean (± SD) | 5.37 | (±6.06) | 3.11 | (± 5.85) | .005 | | |
| Leukocytes (× $10^9$/L) | | | | | | | |
| Mean (± SD) | 9.12 | (±3.96) | 10.22 | (±5.12) | .089 | | |
| CRP (mg/L) | | | | | | | |
| Mean (± SD) | 57.36 | (±76.34) | 53.64 | 85.28 | .741 | | |
| Albumin (g/l) | | | | | | | |
| mean (± SD) | 27.72 | (±8.01) | 32.51 | (±77.1) | <.001 | | |
| Number of contacts | | | | | | | |
| Mean (± SD) | 1.43 | (±0.89) | | | | | |
| Number of contact days | | | | | | | |
| Mean (± SD) | | | 4.35 | (±4.89) | | | |
| Median (range) | | | 3 | (1–37) | | | |
| Outcome | | | | | | | |
| Transferal to another hospital | 24 | 25.8% | 55 | 41.4% | .016 | 0.493 | .277–.880 |
| Discharge | 61 | 65.6% | 72 | 54.1% | .085 | 1.615 | .934–2.791 |
| Death | 8 | 8.6% | 6 | 4.5% | .209 | 1.992 | .667–5.946 |

Abbreviations: CI, confidence interval; CRP, C-reactive protein; ICU, intensive care unit; OR, odds ratio; SD, standard deviation.

**Table 2. Laboratory Findings and Exposure Days for All Index-Contact Pairs With Possible Transmission (Proven Transmission Highlighted in Grey)**

| Pair | | Index | Contact | Match PFGE | Exposure days |
|---|---|---|---|---|---|
| 1 | Species | *E. coli* | *E.coli* | 11% | 9 |
| | PCR | other than CTX-M | other than CTX-M | | |
| 2 | Species | *E. coli* | *E. coli* | 92.6% | 10 |
| | PCR | CTX-M | CTX-M | | |
| 3 | Species | *E. coli* | *E. coli* | 23.7% | 3 |
| | PCR | CTX-M | CTX-M | | |
| 4 | Species | *E. coli* | *E. coli* | 11.0% | 13 |
| | PCR | CTX-M | CTX-M | | |
| 5 | Species | *E. coli* | *E. coli* | 11.0% | 6 |
| | PCR | CTX-M | other than CTX-M | | |
| 6 | Species | *K. pneumoniae* | *K. pneumoniae* | 95.7% | 9 |
| | PCR | CTX-M | CTX-M | | |
| 7 | Species | *E. coli* | *E. coli* | 18.5% | 3 |
| | PCR | CTX-M | CTX-M | | |

Abbreviatons: PCR, polymerase chain reaction; PFGE, pulsed-field gel electrophoresis.

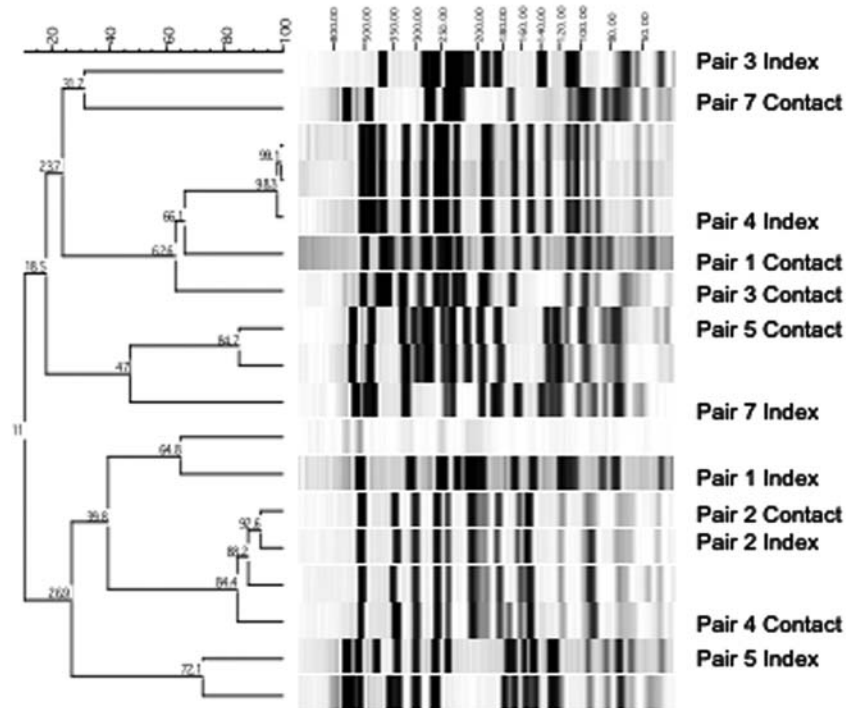


**Figure 1.** Pulsed-field gel electrophoresis for index-contact pairs 1–5 and 7 with detection of *Escherichia coli.* The strains in the lanes not labelled were detected in patients not included in our study (ie, strains sent to the microbiology laboratory from other institutions or strains from patients at our institutions who had no contacts or were only seen as outpatients). Abbreviation: PFGE, pulsed-field gel electrophoresis.

lead to a single infection during a >10-year period, involving >300 000 inpatients at our University Hospital.

Epidemiological surveillance and molecular typing did not provide any evidence for a common source or outbreak during the study period.

## DISCUSSION

During an 11-year and 10-month study period, 133 contact patients, accounting for 579 contact days, were identified. With use of standard precautions, 2 transmissions of ESBL-producing Enterobacteriaceae were identified, both resulting in colonization, but not infection, of the contact patient. Our results therefore suggest that standard precautions may be sufficient and contact isolation may not be required for ESBL-producing *E. coli*–colonized or infected patients, even in intensive care units. These results provide evidence that the low rate of transmission does not justify the additional resources for contact isolation. ESBL-producing Enterobacteriaceae are emerging in all parts of the world and are common in Europe.

**Figure 2.** Pulsed-field gel electrophoresis for index-contact pair 6 with detection of *Klebsiella pneumoniae.* Abbreviation: PFGE, pulsed-field gel electrophoresis.

The dissemination of high-risk strains, such as the global ST131 *E. coli* clone often harbouring CTX-M-15 ESBLs, which has been isolated from non-human sources, including farm and companion animals, river water, and foods [14], and widespread use of antibiotics in both humans and animals may be the more important drivers for the spread of these drug-resistant pathogens [15], compared with nosocomial transmission. The low level of transmission detected in this study challenges the current policy of contact isolation, rapidly exceeding the capacity of isolation rooms in many hospitals. Therefore, the policy of applying standard precautions for ESBL-producing *E. coli* appears to be a reasonable step to balance risk of transmission and allocation of resources.

Several issues should be considered before moving to standard precautions. Our results are applicable to the sporadic setting or a setting of endemicity and may not be useful during an outbreak or epidemic. Because most ESBL-producing gram-negative pathogens were *E. coli*, these results cannot be extrapolated to non–*E. coli* strains. The small sample size of the latter group does not allow for meaningful conclusions. A distinction between *E. coli* and non–*E. coli* ESBLs is also supported by the fact that >90% of chicken meat [16, 17] and almost 20% of Swiss pork may be contaminated with *E. coli* ESBLs [18]. The predominant ESBL genotype in chicken meat and pork was CTX-M. Therefore, increasing evidence suggests that spread of ESBL-producing *E. coli* relates more to the food chain than to nosocomial transmission in health care settings.

Furthermore, we cannot exclude that the low rate of transmission at our institution may be attributable to a high level of infection control standards, with continuing education and surveillance of hand hygiene being a major focus [19]. Socioeconomic status, most probably reflecting poor hygiene, has been revealed as an independent risk factor for ESBL carriage [20].

The nosocomial transmission rate of highly drug-resistant gram-negative bacteria was also found to be relatively low in a large multi-center trial involving 18 Dutch hospitals that, however, did not involve active screening procedures of contact patients [21]. The adjusted transmission index, the ratio of secondary to primary cases, in the participating hospitals ranged from 0.0 to 0.2. The authors also concluded that well-established transmission-based precautions were used in all enrolled hospitals.

Contact isolation has been well established for control of transmission of multidrug-resistant gram-positive organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococci (VRE) [22, 23]. These pathogens survive for days and weeks on surfaces, whereas Enterobactericeae do not survive for prolonged periods on dry surfaces [24]. In addition, psoriasin on the human skin can kill *E. coli*, but carriage of *S. aureus* is observed in more than one-third of the population [25]. Both transmissions, which occurred in our study, may have been attributable to patients sharing the same bathroom, with humidity facilitating survival of gram-negatives bacteria on surfaces that are generally not viable after drying [26].

Secondary end points of the study were length of hospital stay, number of underlying diseases, number of previous hospital stays, and mean albumin level at admission, which differed significantly between patients infected or colonized with ESBL-producing Enterobacteriaceae and contact patients, a finding previously reported in the literature [27, 28]. Schoevaerdts et al reported a high prevalence of major comorbidities in a descriptive analysis of 114 consecutive patients with recovery of ESBL-positive Enterobacteriaceae [28]. The significantly lower mean albumin level detected in our study for index patients, compared with contacts, possibly reflects poorer health conditions of patients colonized or infected with ESBL-producing Enterobacteriaceae. Because length of hospital stay and number of previous hospital stays were greater in this study for index patients, one could hypothesize that there is a role of nosocomial transmission in acquiring ESBL-producing Enterobacteriaceae. However, our data collected over an 11-year study period do not support this assumption. Increased exposure to antibiotics because of the comorbid state (resulting in selection pressure in colonized patients), reflected by longer and numerous hospitalizations, could explain these findings. Unfortunately, we were not able to obtain information on prior antibiotic exposure to support this assumption in our study.

Important limitations of our study are its observational design and that it was conducted at a single center. However, randomized controlled clinical trials over several years are rarely sponsored and are difficult to perform. Only one clinical trial (NCT00976638) is listed in the National Institutes of Health–sponsored database on transmission of multidrug-resistant pathogens, including ESBL in intensive care units, also an observational clinical trial. The true extent of transmission may have been underestimated, because the ESBL-encoding genes are mostly located on mobile genetic elements, such as plasmids and could therefore have been transferred to other Enterobacteriaceae. However, because of the small number of positive screening results of contact patients, we do not believe that this limitation questions the findings and conclusions of our study. Moreover, the detection method could have missed some ESBL strains in contact patients. However, we used standard selective culture methods, and chromogenic agar plates selectively for ESBL screening were not available at the beginning of the study. Because the vast majority of ESBL producers at our institution are *E. coli*, our results may not be generalizable to other Enterobacteriaceae. Furthermore, only hospitalized patients were included; therefore, results may not be extrapolated to an outpatient setting or to healthy

individuals. However, the burden of contact isolation is mainly an issue in hospitals rather than in the outpatient setting. Finally, our results are applicable to acute care with short-term hospitalization (≤5 days) and to institutions with a high standard of standard precautions (especially hand hygiene) and low numbers of beds per room (1–2 beds per room). The rate of transmission may be different in prolonged hospitalization and requires another study design.

We conclude that the rate of transmission of ESBL-producing Enterobacteriaceae—in particular, *E. coli*—is very low in our large tertiary care center, challenging the current concept of routine contact isolation of patients infected with ESBL-producing *E. coli*, the most common pathogen harbouring ESBL. Omitting contact isolation in these cases could save resources and potentially improve patient care and comfort. This approach is also supported by the fact that ESBL-producing *E. coli* has been found in many food items [16, 17, 18].

## Notes

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***Potential conflicts of interest.*** All authors: No reported 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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