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Susceptibility of *Klebsiella pneumoniae* Isolates from Intra-Abdominal Infections and Molecular Characterization of Ertapenem-Resistant Isolates[▽]

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A total of 2,841 clinical isolates of *Klebsiella pneumoniae* from intra-abdominal infections worldwide were collected in the Study for Monitoring Antimicrobial Resistance Trends (SMART) during 2008 and 2009. Overall, 22.4% of isolates had extended-spectrum β-lactamases (ESBLs). The most active antibiotics among the 11 tested were imipenem, amikacin, and ertapenem, though even these, like all other comparators, were less consistently active against ESBL-positive isolates than against ESBL-negative isolates. Globally, 6.5% of isolates were ertapenem resistant based on the June 2010 clinical breakpoints published by the Clinical and Laboratory Standards Institute, with MICs of ≥1 μg/ml. Molecular characterization of 43 isolates with ertapenem MICs of ≥4 μg/ml showed that they variously produced CTX-M or SHV ESBLs combined with altered impermeability and/or had KPC ($n = 28$), OXA-48 ($n = 3$), or VIM ($n = 1$) carbapenemases. Further monitoring of ertapenem susceptibility and molecular characterization of ertapenem-resistant isolates are needed.

Intra-abdominal infections (IAIs) are among the most frequently encountered infections in health care settings (17, 34). Failure to diagnose these infections early, as well as inadequate treatment, has been associated with increased rates of clinical failure and mortality (1, 9, 21, 29, 38).

Several agents are recommended by the Infectious Diseases Society of America (IDSA) as monotherapy for the treatment of IAIs, including ertapenem, imipenem, meropenem, and piperacillin-tazobactam. Cephalosporins and fluoroquinolones are recommended for use in combination with metronidazole (30). The Study for Monitoring Antimicrobial Resistance Trends (SMART) has been monitoring the susceptibility of Gram-negative bacilli (GNB) from IAIs to ertapenem and comparators since 2002, with nearly 170 hospitals participating worldwide (13).

Numerous reports describe the occurrence of ertapenem resistance in *Klebsiella pneumoniae*. This has been linked to a variety of molecular mechanisms, including the combination of CTX-M and other extended-spectrum β-lactamases (ESBLs) or AmpC with porin loss and with the presence of various carbapenemases, including KPC, NDM, VIM, and OXA-48 enzymes (10, 11, 14, 20, 26, 27, 36, 37). Fewer reports describe global, regional, or local regional prevalence rates of ertapenem resistance; the current SMART report therefore addresses this topic and describes ertapenem resistance rates in *K. pneumoniae* isolated from IAI in 2008 and 2009.

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MATERIALS AND METHODS

Study isolates. All isolates in the study were from IAIs, and only one isolate per species per patient was accepted. Up to 100 consecutive nonselected Gram-negative aerobic and facultative bacilli from each of 138 participating hospitals (Africa, 3; Asia, 32; Europe, 44; Latin America, 19; Middle East, 3; North America, 30; and South Pacific, 7) were cultured from intra-abdominal body sites (e.g., appendix, peritoneum, colon, bile, pelvis, and pancreas). The majority of intra-abdominal specimens were obtained during surgery, though some paracentesis specimens were also accepted. Isolates from blood, urine, and perirectal abscesses were excluded. All organisms were deemed clinically significant based upon the criteria of the local investigators. Isolate inclusion was independent of antimicrobial use, age, or gender. Overall, 2,841 isolates of *K. pneumoniae* were collected during 2008 and 2009 from the 138 hospitals. The isolates were identified to the species level at each site and sent to a central laboratory (Laboratories International for Microbiology Studies, a subsidiary of International Health Management Associates, Inc., Schaumburg, IL) for confirmation of identification and antimicrobial susceptibility testing. International Health Management Associates, Inc., managed the development of a centralized database of study results.

Susceptibility testing. MICs were determined using MicroScan dehydrated broth microdilution panels (Siemens Medical Solutions Diagnostics, West Sacramento, CA), following Clinical and Laboratory Standards Institute (CLSI) and manufacturer's guidelines (3). The following antimicrobial agents (with their dilution ranges expressed in μg/ml) were included on the panels: ertapenem (0.03 to 4), imipenem (0.06 to 8), cefepime (0.5 to 32), ceftazidime (0.5 to 128), ceftazidime-clavulanic acid (0.12 to 16), cefoxitin (2 to 16), ciprofloxacin (0.25 to 2), amikacin (4 to 32), levofloxacin (0.5 to 4), cefotaxime (0.5 to 128), cefotaxime-clavulanic acid (0.12 to 16), piperacillin-tazobactam (2/4 to 64/4), ampicillin-sulbactam (2/2 to 16/2), and ceftriaxone (1 to 32). MICs were interpreted following CLSI guidelines (4), including the new clinical breakpoints published in 2010 for carbapenems. According to the new carbapenem breakpoints, resistances to ertapenem and imipenem are defined as MICs of ≥1 and ≥4 μg/ml, respectively (5).

ESBL designation. Following CLSI guidelines, *K. pneumoniae* isolates were classified as ESBL producers if there was at least an 8-fold reduction (i.e., three doubling dilutions) of the MIC for ceftazidime or cefotaxime in combination with clavulanic acid versus their MICs when tested alone (4).

Molecular characterization. DNA was extracted from overnight colonies grown on blood agar (Remel, Lenexa, KS) using the QIAamp DNA minikit and

TABLE 1. Numbers of *K. pneumoniae* isolates by region and ESBL status

Region	No. of isolates			
	Total	ESBL$^-$	ESBL$^+$	% ESBL$^+$
Global	2,841	2,204	637	22.4
Asia	1,013	754	259	25.6
Europe	671	539	132	19.7
North America	500	450	50	10
Latin America	410	268	142	34.6
South Pacific	154	124	30	19.5
Middle East	62	48	14	22.6
Africa	31	21	10	32.2

the QIAcube instrument (Qiagen, Valencia, CA). PCR for characterization of ESBL genes was carried out in an ABI 9700 thermocycler (Applied Biosystems, Carlsbad, CA). *bla* genes for TEM, SHV, CTX-M, OXA-48, metallo-type (IMP, VIM, SPM, SIM, GIM, and NDM), and KPC-type enzymes were amplified as previously described (7, 20, 24, 29, 33, 37). PCR was carried out with the Fast Cycling PCR kit (Qiagen, Valencia, CA). Purification of the PCR products was performed using the Exo-SAP-IT reagent (USB, Cleveland, OH). PCR-amplified fragments were sequenced using the ABI 3730XL DNA analyzer (Applied Biosystems, Carlsbad, CA). Nucleotide sequences were analyzed with the SeqScape, version 7.0, software program (Applied Biosystems, Carlsbad, CA) and compared with sequences available at the National Center for Biotechnology Information website (www.ncbi.nlm.nih.gov). Multiplex amplification of pAmpC genes was performed as previously described by Perez-Perez and Hanson (26). Outer membrane proteins (OMPs) were extracted and analyzed as previously described (6).

QC. Quality control (QC) was performed each day of testing using the CLSI-recommended QC strains *Escherichia coli* ATCC 25922, *E. coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 27853, and *K. pneumoniae* ATCC 700603 (ESBL-positive control). Results for isolates were included in the analysis only when corresponding QC strains tested within the acceptable ranges according to CLSI guidelines (4).

Nucleotide sequence accession number. The DNA sequence encoding KPC-11 has been allocated GenBank accession no. HM066995.

RESULTS

Table 1 shows the distribution of the 2,841 clinical isolates by geographical region and ESBL status. The majority of the isolates were from Asia and Europe, reflecting the larger number of participating hospitals in these regions. Prevalence rates of ESBL-positive *K. pneumoniae* ranged from 10% in North America to 34.6% in Latin America; globally, the ESBL rate was 22.4% (Table 1).

Table 2 describes the global activities of ertapenem and its 11 comparators against the pool of all isolates and against the subgroups with and without ESBLs. Against all isolates (n = 2,841), the most active agents were imipenem, amikacin, and ertapenem, with 96.1, 92.3, and 91.6% of isolates susceptible, respectively. Susceptibility rates were lower for all agents against the ESBL producers (n = 637) but still highest for imipenem, ertapenem, and amikacin at 91.1, 77.9, and 76.1%, respectively. ESBL-negative isolates (n = 2,204) were generally more susceptible to all agents, with only ampicillin-sulbactam and ciprofloxacin active against fewer than 90%. For the carbapenems, the use of the two different CLSI breakpoints caused a general lowering of susceptibility to both ertapenem and imipenem.

Rates of susceptibility to ertapenem varied between the different geographical regions, from 82.3% (Middle East) to 100% (Africa), though the numbers of isolates in these two particular regions were relatively small (<100 isolates each) (Table 3). For regions submitting >100 isolates, rates of susceptibility to ertapenem ranged from 89.4% (Asia; n = 1,013) to 96% (North America; n = 500). Against ESBL-positive isolates (n > 100), ertapenem susceptibility rates ranged from 71.2% (Europe; n = 132) to 83.9% (Latin America; n = 142). Susceptibility rates for ESBL-negative isolates ranged from 92.8% (Asia; n = 754) to 98.4% (North America; n = 450) (Table 3).

Among all 2,841 isolates in the study, 6.5% were resistant to ertapenem at the new CLSI resistance breakpoint of ≥1 μg/ml and 1.9% were intermediate; the MIC range was ≤0.03 to >4 μg/ml. Excluding regions with low contribution rates (Africa and the Middle East), the prevalence of ertapenem resistance was 7.9% in Asia (80 of 1,013 isolates; 25 hospital sites), 7.1% in the South Pacific region (11 of 154 isolates; 2 hospital sites), 7% in Europe (147 of 671 isolates; 19 hospital sites), 4.4% in Latin America (18 of 410 isolates; 10 hospital sites), and 3.8% in North America (19 of 500 isolates; 6 hospital sites).

Molecular mechanisms of resistance were examined in all 43 isolates that exhibited ertapenem MICs of ≥4 μg/ml (Table 4). The six isolates with ertapenem MICs of 4 μg/ml originated in four countries: Greece (1 isolate), Spain (1 isolate), Taiwan (1 isolate), and Turkey (3 isolates). One isolate had SHV-12 and OXA-48 enzymes, one had a TEM-12 enzyme along with OMP changes suggesting reduced permeability, two had both CTX-M-15 and OXA-48 enzymes, and two had SHV-5/12 enzymes along with OMP changes suggesting reduced permeability. All of these six isolates were AmpC negative.

The 37 isolates with ertapenem MICs of >4 μg/ml were from 13 countries: Argentina (1 isolate), Chile (2 isolates), Colombia (2 isolates), Germany (1 isolate), Greece (14 isolates), Israel (4 isolates), Italy (1 isolate), Philippines (1 isolate), Puerto Rico (1 isolate), Taiwan (1 isolate), Thailand (1 isolate), Turkey (1 isolate), and the United States (7 isolates). Twenty-eight (76%) of these isolates had KPC carbapenemases, six of these possessed KPC-3 only, and three had only KPC-2 (Table 4) and lacked ESBLs. The remaining 19 were positive for KPC-2, -3, or -11 and also had SHV-12 and -5 ESBLs. KPC-11 is a novel variant. The isolates with KPC enzymes originated from Colombia (2 isolates), Greece (14 isolates), Israel (4 isolates), Puerto Rico (1 isolate), and the United States (7 isolates). One isolate among the 37 with ertapenem MICs of >4 μg/ml was from Turkey and produced SHV-12 and CTX-M-3 ESBLs, along with a VIM-1 carbapenemase; another from Turkey had only an OXA-48 carbapenemase. Of the nine isolates without KPCs, most were positive for CTX-M (CTX-M-2, -3, -15, or -14) with reduced permeability; these were from Chile (2 isolates), Germany (1 isolate), Argentina (1 isolate), Italy (1 isolate), Philippines (1 isolate), Taiwan (1 isolate), Thailand (1 isolate), and Turkey (1 isolate). Of these, five lacked both Omp-K35 and Omp-K36, whereas the others lack only one or the other of these porins.

DISCUSSION

The current study confirms the results of previous SMART reports (12, 13, 15, 16) showing that carbapenems and amikacin remain the most active agents against *K. pneumoniae* isolated in IAIs. Tigecycline and polymyxins were not tested as

TABLE 2. Global susceptibilities of *K. pneumoniae* isolates to ertapenem and comparators[a]

Isolate group (n^b) and drug[c]	MIC_{50}	MIC_{90}	%S	%I	%R	Min	Max
All (2,841)							
Amikacin	≤4	16	92.3	3.0	4.7	≤4	>32
Ampicillin-sulbactam	8	>16	58.3	9.5	32.2	≤2	>16
Cefepime	≤0.5	>32	79.1	0.7	20.1	≤0.5	>32
Cefotaxime	≤0.5	>128	73.6	0.5	25.9	≤0.5	>128
Ceftazidime	≤0.5	>128	76.0	1.4	22.6	≤0.5	>128
Ceftriaxone	≤1	>32	73.3	0.7	26.0	≤1	>32
Ciprofloxacin	≤0.25	>2	73.7	2.1	24.3	≤0.25	>2
Ertapenem (new Bp)	**≤0.03**	**0.25**	**91.6**	**1.9**	**6.5**	**≤0.03**	**>4**
Ertapenem (old Bp)	≤0.03	0.25	95.5	0.6	3.9	≤0.03	>4
Imipenem (new Bp)	**0.25**	**0.5**	**96.1**	**0.7**	**3.2**	**≤0.06**	**>8**
Imipenem (old Bp)	0.25	0.5	97.4	1.1	1.5	≤0.06	>8
Levofloxacin	≤0.5	>4	79.1	3.0	17.9	≤0.5	>4
Piperacillin-tazobactam	≤2	>64	80.0	6.3	13.7	≤2	>64
$ESBL^+$ (637)							
Amikacin	≤4	>32	76.1	10.5	13.3	≤4	>32
Ampicillin-sulbactam	>16	>16	2.2	9.7	88.1	4	>16
Cefepime	>32	>32	16.0	2.5	81.5	≤0.5	>32
Cefotaxime	>128	>128	2.4	0.0	97.7	≤0.5	>128
Ceftazidime	128	>128	10.2	4.4	85.4	≤0.5	>128
Ceftriaxone	>32	>32	2.2	0.2	97.7	≤1	>32
Ciprofloxacin	>2	>2	22.1	5.2	72.7	≤0.25	>2
Ertapenem (new Bp)	**0.12**	**>4**	**77.9**	**5.5**	**16.6**	**≤0.03**	**>4**
Ertapenem (old Bp)	0.12	>4	88.1	1.9	10.0	≤0.03	>4
Imipenem (new Bp)	**0.25**	**1**	**91.1**	**1.1**	**7.9**	**≤0.06**	**>8**
Imipenem (old Bp)	0.25	1	93.7	3.8	2.5	≤0.06	>8
Levofloxacin	>4	>4	37.7	8.3	54.0	≤0.5	>4
Piperacillin-tazobactam	32	>64	42.2	19.5	38.3	≤2	>64
$ESBL^-$ (2,204)							
Amikacin	≤4	≤4	97.0	0.8	2.2	≤4	>32
Ampicillin-sulbactam	8	>16	74.6	9.4	16.1	≤2	>16
Cefepime	≤0.5	≤0.5	97.4	0.2	2.4	≤0.5	>32
Cefotaxime	≤0.5	≤0.5	94.2	0.6	5.2	≤0.5	>128
Ceftazidime	≤0.5	1	95.0	0.5	4.5	≤0.5	>128
Ceftriaxone	≤1	≤1	93.9	0.9	5.3	≤1	>32
Ciprofloxacin	≤0.25	>2	88.6	1.2	10.3	≤0.25	>2
Ertapenem (new Bp)	**≤0.03**	**≤0.03**	**95.5**	**0.9**	**3.6**	**≤0.03**	**>4**
Ertapenem (old Bp)	≤0.03	≤0.03	97.5	0.3	2.2	≤0.03	>4
Imipenem (new Bp)	**0.25**	**0.5**	**97.5**	**0.6**	**1.9**	**≤0.06**	**>8**
Imipenem (old Bp)	0.25	0.5	98.4	0.4	1.2	≤0.06	>8
Levofloxacin	≤0.5	2	91.1	1.5	7.4	≤0.5	>4
Piperacillin-tazobactam	≤2	16	90.9	2.5	6.6	≤2	>64

[a] S, susceptible; I, intermediate; R, resistant; Min, ●●●; Max, ●●●. Boldface indicates new breakpoints.
[b] *n*, no. of isolates.
[c] New Bp, new breakpoints as defined in CLSI M100-S20-U (June 2010, updated): ertapenem, S, I, R = ≤0.25, 0.5, ≥1 μg/ml; imipenem, S, I, R = ≤1, 2, ≥4 μg/ml. Old Bp, old breakpoints as defined in CLSI M100-20 (January 2010): ertapenem, S, I, R = ≤2, 4, ≥8 μg/ml; imipenem, S, I, R = ≤4, 8, ≥16 μg/ml.

part of the SMART antibiotic testing panel but are also likely to have been active against many of the isolates. It is noteworthy that compared with findings in previous SMART reports concerning data from 2002 to 2008, susceptibilities to most agents continued to decline, though the susceptibility decrease for the carbapenems and amikacin was smaller. Nevertheless, and unlike the case in earlier years, the current study shows a worldwide distribution of ertapenem-resistant (MIC > 0.5 μg/ml) *K. pneumoniae* isolates. These now accounted for 6.5% of all *K. pneumoniae* isolates over multiple countries and geographical regions, with 8.4% nonsusceptible (MIC > 0.25 μg/ml). This shift substantially reflects the new, lower June 2010 CLSI breakpoints for carbapenems (5). If the previous CLSI breakpoints for ertapenem were used (resistant, >4 μg/ml; susceptible, ≤2 μg/ml), only 3.9% of the isolates would be counted as resistant and 4.5% as nonsusceptible. Under both the new and old criteria, resistance rates were higher among ESBL producers (16.6% and 10.0%, respectively) than among nonproducers (3.6 and 2.2%, respectively).

The new breakpoints also increased the proportion counted as nonsusceptible to imipenem, though less so than for ertapenem. Thus, 3.9% of all isolates, 9.0% of ESBL producers, and 2.5% of ESBL-negative isolates now were counted as nonsusceptible compared to 2.6, 6.3, and 1.6%, respectively, using the previous CLSI criteria ($P < 0.01$).

The increased resistance rate also reflects the spread of carbapenemases, and on this basis, isolates with MICs of ≥4 μg/ml were further investigated to determine the molecular

TABLE 3. Regional susceptibilities of *K. pneumoniae* isolates to ertapenem[a]

Isolate group (n^b) and region	No. of isolates	MIC_{50}	MIC_{90}	%S	%I	%R
All (2,841)						
Africa	31	≤0.03	0.06	100.0	0.0	0.0
Asia	1,013	≤0.03	0.5	89.4	2.7	7.9
Europe	671	≤0.03	0.25	91.7	1.3	7.0
Latin America	410	≤0.03	0.25	92.5	2.9	4.6
Middle East	62	≤0.03	>4	82.3	1.6	16.1
North America	500	≤0.03	0.06	96.0	0.2	3.8
South Pacific	154	≤0.03	0.25	90.3	2.6	7.1
Global	2,841	≤0.03	0.25	91.6	1.9	6.5
$ESBL^+$ (637)						
Africa	10	≤0.03	0.12	100.0	0.0	0.0
Asia	259	0.12	2	79.5	5.8	14.7
Europe	132	0.12	>4	71.2	3.0	25.8
Latin America	142	0.12	0.5	83.9	7.7	8.4
Middle East	14	0.06	>4	78.6	7.1	14.3
North America	50	0.12	>4	74.0	0.0	26.0
South Pacific	30	0.12	2	63.3	13.3	23.3
Global	637	0.12	>4	77.9	5.5	16.6
$ESBL^-$ (2,204)						
Africa	21	≤0.03	≤0.03	100.0	0.0	0.0
Asia	754	≤0.03	0.12	92.8	1.6	5.6
Europe	539	≤0.03	≤0.03	96.7	0.9	2.4
Latin America	268	≤0.03	0.06	97.0	0.4	2.6
Middle East	48	≤0.03	>4	83.3	0.0	16.7
North America	450	≤0.03	≤0.03	98.4	0.2	1.3
South Pacific	124	≤0.03	0.06	96.8	0.0	3.2
Global	2,204	≤0.03	≤0.03	95.5	0.9	3.6

[a] See footnote *a* of Table 2 for abbreviations.
[b] *n*, no. of isolates.

TABLE 4. Molecular mechanisms of resistance in isolates with ertapenem MICs of ≥4 μg/ml

MIC and mechanism(s)	No. of isolates	Country
Ertapenem MIC = 4 μg/ml		
CTX-M-15 + OXA-48	2	Turkey
SHV-12 + OXA-48	1	Turkey
SHV-12 + altered permeability	1	Spain
SHV-5 + altered permeability	1	Greece
TEM-12 + altered permeability	1	Taiwan
Ertapenem MIC > 4 μg/ml		
KPC^+	28	
KPC-2 only	3	Colombia, Puerto Rico, USA
KPC-2 + SHV-12	11	Greece, Israel, USA
KPC-2 + SHV-5	1	Greece
KPC-2 + SHV-12 + CTX-M-32	1	Greece
KPC-3 only	6	Colombia, Israel, USA
KPC-3 + SHV-12	2	USA
KPC-11 + SHV-12	4	Greece
KPC^-	9	
CTX-M-15 + altered permeability	3	Chile, Italy, Thailand
CTX-M-3 + altered permeability	2	Germany, Philippines
CTX-M-3 + VIM + SHV-12	1	Turkey
CTX-M-2 + altered permeability	1	Chile
CTX-M-14 + AmpC + altered permeability	1	Taiwan
OXA-48	1	Argentina

mechanisms conferring resistance to ertapenem. The six isolates with MICs of 4 μg/ml variously had SHV, TEM, and CTX-M ESBLs, together with OMP changes, or had OXA-48 carbapenemase; all were AmpC and KPC negative. Among the 37 isolates with ertapenem MICs of >4 μg/ml, 28 (76%) had KPC enzymes and 2 had VIM or OXA-48 carbapenemases. The remaining 7 mostly had CTX-M-enzymes along with reduced permeability.

KPC enzymes are now well known, and isolates positive for KPC-2 and -3 have previously been observed in the same countries or territories as in the current report, including Colombia, Greece, Israel, Puerto Rico, and the United States (2, 8, 23, 24, 25). The new variant reported here (KPC-11) was found in four isolates from Greece. Carbapenem resistance is also well known in *K. pneumoniae* with reduced permeability, owing to altered or reduced levels of OmpK35 and OmpK36 (6, 10) along with an ESBL or AmpC enzyme. The current SMART report identifies several such isolates from Chile, Germany, Greece, Italy, Spain, Taiwan, and Thailand, in which the enzyme present was CTX-M-2, -3, -14, or -15, SHV-5 or SHV-12, or TEM-12 combined with a loss of permeability.

Isolates with metallo-beta-lactamase-mediated resistance to ertapenem appear to be less common overall. Notable exceptions are VIM, prevalent in Greece, perhaps reflecting the heavy use of carbapenems (28), and NDM, which is widely reported on the Indian subcontinent (18). The single VIM-producing isolate detected in the present study was from Turkey.

A few isolates had an OXA-48 enzyme and were associated with ertapenem MICs of ≥4 μg/ml. Only one of these expressed OXA-48 alone, whereas the others also had SHV or CTX-M-15 ESBLs. OXA-48 has been shown to play a role in the expression of carbapenem resistance in *K. pneumoniae* (6, 19, 33) and is widespread in Turkey, which was the source of three of the present four OXA-48 producer isolates, the exception being an isolate from Argentina.

In summary, the data from the 2008-2009 SMART report show that while the carbapenems ertapenem and imipenem and also amikacin remain the most active agents against clinical isolates of *K. pneumoniae*, a subpopulation of ertapenem-resistant organisms is now present. The increased prominence of this group partly reflects the lowering of clinical breakpoints but also indicates the spread of carbapenemases, principally KPC types. Similarly, data from the United States Centers for Disease Control and Prevention have shown an increase in carbapenem-resistant *K. pneumoniae* from <1% in 2000 to 8% in 2007 (32). Further monitoring of the susceptibility of *K. pneumoniae* and characterization of the resistance mechanisms are clearly warranted for accurate documentation of carbapenem resistance trends in this species.

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We are responsible for the work described in this article. All authors were involved in at least one of the following: conception, design, acquisition, analysis, statistical analysis, interpretation of data, and

drafting the manuscript and/or revising the manuscript for important intellectual content. All authors provided final approval of the version to be published.

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