Evaluation of the Antimicrobial Susceptibility of Community-Acquired Urinary Tract Infection

ARTIGO ORIGINAL

Avaliação do Perfil de Sensibilidade aos Antibióticos na Infeção Urinária da Comunidade

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ABSTRACT

Introduction: The urinary tract infections, after respiratory infections, are the most common in the community. The knowledge about the prevalence of microbial strains and their antibiotic susceptibility is crucial to establish an effective empirical therapy. The aim of this study was to determine the antibiotic susceptibility patterns of bacterial strains isolated from positive urine cultures performed in patients from the central region of Portugal.

Material and Methods: We carried out a documental analysis of 6008 urine bacteriological exams, to be made available to physicians, most of which run through the automated system VITEK 2, bioMérieux. The majority (80%) of the urine bacteriological exams were from female. Escherichia coli was the most prevalent bacterial pathogen (65.9%), followed by Klebsiella spp (12%).

Results: Nitrofurantoin showed high levels of activity (96%) for *Escherichia coli*, as well as Fosfomycin (96.6%). Amoxicillin-clavulanic acid presents an activity level of only 81.1% for the same germ. Quinolones exhibit efficacy to only 78% of the strains of *Escherichia coli*, below the Fosfomycin and Nitrofurantoin. Nitrofurantoin showed high levels of activity (96%) for *E. coli* as well as Fosfomycin (96.6%). Amoxicillin-Clavulanic Acid presents a level of activity of only 81.1% for the same germ. The quinolones have a efficacy for only 78% of strains of *E. coli*, lower than Fosfomycin.

Discussion: *Escherichia Coli* was the most prevalent uropathogen (65.9%). High efficacy against this pathogenic agent was found for Fosfomycin (96.6%) and Nitrofurantoin (96%).

Conclusion: Further antimicrobial surveillance studies should be developed, in order to formulate local empirical therapy recommendations for optimized therapeutical choices.

Keywords: Urinary Tract Infections; Drug Resistance, Bacterial; Anti-Bacterial Agents; Community-Acquired Infections.

RESUMO

Introdução: As infeções do trato urinário, depois das infeções respiratórias, são as mais comuns na comunidade. O conhecimento sobre a prevalência das estirpes microbianas e a sua suscetibilidade aos antibióticos é fundamental para instituir uma terapêutica empírica eficaz. O objetivo deste estudo foi determinar os padrões de suscetibilidade aos antibióticos das estirpes bacterianas isoladas em uroculturas positivas efetuadas em doentes da região centro de Portugal.

Material e Métodos: Procedemos a uma análise documental dos 6008 resultados de uroculturas, a disponibilizar aos médicos no ano de 2013, a maioria das quais executadas através do sistema automatizado VITEK 2 da bioMérieux. A análise dos dados foi efetuada através do SPSS versão 21.

Resultados: A maioria (80%) das 6008 uroculturas positivas foi efetuada no sexo feminino. A *Escherichia coli* foi a bactéria mais prevalente na amostra (65,9%), seguida pela *Klebsiella spp* (12%). A Nitrofurantoína apresentou elevada eficácia (96%) para as estirpes de *E. coli*, bem como a Fosfomicina (96,6%). A Amoxicilina-Ácido Clavulânico apresentou um nível de eficácia de apenas 81,1%, para o mesmo gérmen. As quinolonas apresentaram eficácia para 78% das estirpes de *E. coli*, sendo inferior à registada para a Fosfomicina e para a Nitrofurantoína.

Discussão: O presente estudo revelou que a *E. coli* foi o agente patogénico predominante nas infeções do trato urinário da comunidade (65,9%) apresentando percentagens de sensibilidade elevadas à Fosfomicina (96,6%) e à Nitrofurantoína (96%).

Conclusão: Recomenda-se a monitorização do perfil sensibilidade dos microrganismos aos antibióticos, de modo a otimizar a terapêutica empírica das ITU.

Palavra-chave: Infeções Urinárias; Resistência aos Antibióticos; Agentes Bacterianos; Infeções Comunitárias Adquiridas.

INTRODUCTION

Antimicrobial resistance (AR) is a natural phenomenon that represents a major threat to Public Health, leading to an increase in healthcare costs, to therapeutic failure and sometimes to death.[1] Its increasing frequency is associated to multiple factors, among which is the indiscriminate use of antibiotics. It is a serious worldwide problem affecting both developed and developing countries.[2]

AR progression promotes multi-drug resistant infections, with a difficult and costly treatment, particularly worrying due to their irreversibility or very low reversibility.

AR was considered by the World Health Organization (WHO) as a priority and therefore, since 2001, global measures have been taken regarding its control, mainly through resistance monitoring, prescriber, health professional and wider public education as well as regulation on antibiotic promotion by the drug industry.[2]

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In Europe, antimicrobial consumption in community patients shows large variations between different countries, with a lower consumption in the North, moderate in the East and high in the South.[3] Consumption is assessed by the defined daily doses (DDD) per 1,000 inhabitants per day (DID).[4] In 2002, France had the highest consumption (32.2 DID) while The Netherlands had the lowest (10.0 DID). Portugal was in third place, with approximately 27 DID.[3] Between 2000 and 2009, the antibiotic consumption in Continental Portugal declined from 24.12 to 22.03 DID.[5]

Quinolone consumption in community patients varied, in 2002, between 3.76 DID in Italy, 3.6 in Portugal and 0.17 in Denmark.[3] However, tetracycline, cephalosporin, sulphonamide and quinolone consumption decreased between 2000 and 2009, with an increase on the use of penicillin associated to beta-lactamase inhibitor.[5] According to the same study, in 2009, a 22.56 DID antibiotic consumption was found in the central region of Portugal.

Urinary tract infections (UTI), following respiratory infections, are the most frequent in community setting, with a higher female incidence.[6]

Bacteria are the major microbial agents responsible for UTI. Aerobic Gram-negative bacteria are most prevalent and *Escherichia coli* (*E. coli*) are responsible for approximately 75 to 90% of acute urinary tract infections, followed by *Staphylococcus*, *Proteus*, *Klebsiella pneumoniae* and *Pseudomonas*. *E. coli* is also the major infectious agent responsible for complicated and uncomplicated pyelonephritis.[7]

A 1997 study involving urine culture data[6] found that *E. coli* was involved in 76.6% of UTI, *Proteus mirabilis* (*P. mirabilis*) in 15.6% and *Klebsiella pneumoniae* in 3.7%. In 2006, the same author found *E. coli* (64.0%) to be the most frequent, followed by *P. mirabilis* (9.3%) and *Enterococcus* (7.4%). Another study by Martins[8] found *E. coli* in 73.3% of UTI, *P. mirabilis* in 7.6%, *Klebsiella pneumoniae* in 10%, *Enterococcus faecalis* in 3.5% and *Pseudomonas aeruginosa* in 3.1%. Another hospital-based study[9] involving 572 samples (144 from in-patients and 428 from out-patients) reported a 68.8% *Escherichia coli* prevalence, 7.9% for *Klebsiella pneumoniae,* 6.1% for *Pseudomonas aeruginosa* and 5.2% for *Proteus mirabilis*. In a study by Linhares *et al.*[10] involving 18,797 positive urine cultures, *E. Coli* was found in 64.5% of the samples, *Staphylococcus aureus* in 6.0%, *P. mirabilis* in 4.7%, *Klebsiella spp* in 4.3%, *Enterococcus faecalis* in 3.6%, *Proteus vulgaris* in 2.7% and *Pseudomonas aeruginosa* in 2.4%.

In a 2009 study[6] involving 2,676 urine cultures, 37.2% of *E. coli* strains were found to be resistant to Tobramycin, 24.7% to Norfloxacin, 20.7% to Ciprofloxacin and 12.7% to Amoxicillin-Clavulanic Acid. *P. mirabilis* showed 21.9% of Ampicillin-resistant strains, 15.6% to Trimethoprim-Sulfamethoxazole, 6.1% to Amoxicillin-Clavulanic Acid and 3% to Nitrofurantoin. *Klebsiella* showed a 12.5% resistance to Cephalexin, 0% to Cefuroxime, 38.5% to Nitrofurantoin and 15.6% to Trimetoprim-Sulfamethoxazole. Linhares *et al.*[10] found a 3.0 % *E. coli* strains resistant to Tobramycin, 14.2% to Norfloxacin, 13.9% to Ciprofloxacin, 7.5% to Amoxicillin-Clavulanic Acid and 6% to Nitrofurantoin.

Antimicrobial resistance increases with consumption. Not unexpectedly, a lower resistance rate is found in the Northern European countries, where consumption is lower.[3]

It is estimated that between 50 to 70% of women present with at least one UTI episode during lifetime and 20 to 30% present recurrent episodes with an indication for empirical antimicrobial therapy[11] UTI therapy is associated to microbiological eradication rates of 90% or above[12] when the decision to prescribe an antibiotic is based in the knowledge of which microbial agents are involved and known sensitivity profile.

Therefore, monitoring of antibiotic sensitivity profile is crucial in order to define empirical antimicrobial therapy.[13] The scarcity of studies gives support to epidemiological research on antimicrobial resistance of most frequent infectious agents to be carried out in community-acquired UTI.

Our study aimed to determine antimicrobial sensitivity profile of major bacteria involved in community-acquired UTI within the geographical community of the *ACES Pinhal Litoral.*

MATERIAL AND METHODS

This is a retrospective, descriptive study based on the results of urine cultures carried out during the year 2013 by the main laboratories in the geographical area of *Pinhal Litoral*. Our sample included 6,008 positive urine cultures (> 100,000 colony forming units - CFU). Strain identification and antibiogram was carried out using a bioMérieux VITEK 2 compact system, with different adequate cards. The bioMérieux mini-API system and the Kirby & Bauer disk diffusion method were used in 10% of the samples.

According to Clinical and Laboratory Standards Institute guidelines,[14] the results were ranked as sensitive (S), intermediate (I) and resistant (R). 'Intermediate' samples were subsequently reclassified as resistant. Patient's gender and age data for each urine culture were also collected.

Antimicrobial sensitivity was evaluated for samples with an overall isolated number of germs above 150. Five microorganisms met this criterion (Table 1).

Statistical analysis used the Statistical Package for the Social Sciences (SPSS) software, version 21 for Windows.

RESULTS

Our sample involved 6,008 positive urine cultures (80% from female patients, 4,911 positive urine cultures).

Average age of patients was 62.8, (± 20.7; 6 months-107 years of age).

UTI distribution by age group shows a higher prevalence above 75 years of age (34.9%), followed by 56 to 75 (30%) and the group above 55 years of age corresponded to 65% of our sample, while the group below 16 corresponded to 1.6% (Fig. 1).

E. coli (65.9%) was the predominant isolate, followed by

Klebsiella pneumoniae (12%), *P. mirabilis* (7%), *E. faecalis* (4.8%), *Pseudomonas aeruginosa* (2.7%), *Morganella* (1.8%) and others (5.7%). *Acinetobacter baumannii* was isolated in 11 samples (0.4%) (Table 1).

Considering the distribution of the three most prevalent strains (*E. coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*) corresponding to 84.9% of our sample, we found that their prevalence is variable according to the patient's age group.

E. coli remains the most prevalent, with 72.4% and 74.6% of strains in the 16-35 and 36-55 age groups, respectively. In the age group above 75, it was present in 55.4% of the samples. *Klebsiella pneumoniae* had 16.3% prevalence in the same age group.

Proteus mirabilis, with overall 7% prevalence, showed 21.6% prevalence in the age group below 16 years of age (Table 2).

Antimicrobial sensitivity was evaluated for the five most prevalent microorganisms, according to the established criteria. The *E. coli* strains were sensitive to Fosfomycin in 96.6% of the samples, 96.0% to Nitrofurantoin, 93.0% to Gentamicin, 99.0% to Imipenem, 96.1% to Amikacin, 94.9% to Ceftriaxone and 91.8% to Ceftazidime. As regards the Amoxicillin-Clavulanic Acid and Ciprofloxacin, 81.1% and 78.4% sensitivity was found, respectively (Table 3).

Klebsiella pneumoniae shows a high percentage of sensitivity to Amikacin (95.7%) and Imipenem (99.5%), with 76.9% sensitivity to Gentamicin and 75.8% to Ceftriaxone. *Proteus* shows a high percentage of sensitivity to Ceftriaxone (96.8%), to Amoxicillin-Clavulanic Acid (87.7%) and to Cefuroxime (87.2%). *Enterococcus faecalis* showed 96% sensitivity to Nitrofurantoin, 79.3% to Ampicillin and 74.5% to Benzilpenicillin. *Pseudomonas* showed 92.3% sensitivity to Amikacin, 86.5% to Gentamicin and 57.1% to Ciprofloxacin. As regards *Morganella*, it showed 94.2% sensitivity to Amikacin and 71.5% to Ceftazidime (Table 3).

The *E. coli* strains showed a high percentage of sensitivity to Fosfomycin in all age groups, lowest in the group above

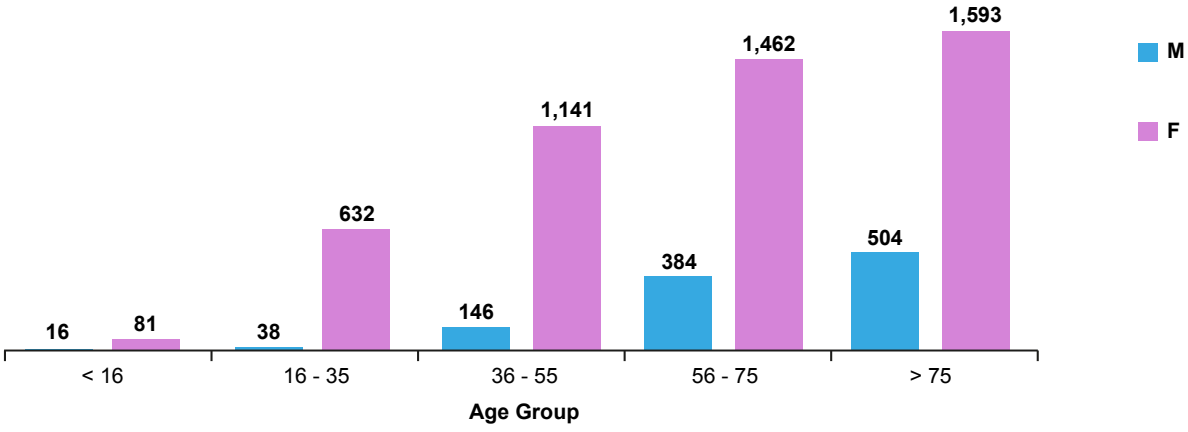

Figure 1 – UTI frequency per age group

Table 1 - Prevalence of bacterial strains

	Male Patients		Female Patients		Total	
Organismo	*n*	%	*n*	%	*n*	%
Escherichia coli	494	12.5	3,465	87.5	3,962	65.9
Klebsiella pneumoniae	165	22.9	554	77.1	719	12.0
Proteus mirabilis	100	23.8	321	76.2	423	7.0
Enterococcus faecalis	105	36.5	183	63.5	288	4.8
Pseudomonas aeruginosa	77	47.2	86	52.8	163	2.7
Morganella	47	44.3	59	55.7	106	1.8
Citrobacter	26	27.1	70	72.9	96	1.6
Enterobacter	15	17.4	71	82.6	86	1.4
Staphylococcus aureus	24	32.4	50	67.6	74	1.2
Providencia stuartii	16	35.6	29	64.4	45	0.7
Serratia marcescens	12	50.0	12	50.0	24	0.4
Acinetobacter baumannii	11	50.0	11	50.0	22	0.4
TOTAL	1,092	20	4,911	80.0	6,008	100.0

75 years of age (93%) (Table 4). The sensitivity test was not performed for this drug during the first trimester of 2013.

Cefuroxime showed a 92.9% efficacy against *E. coli* in patients aged below 55, decreasing to 88% and 79.4% in the 56-75 and > 75 age groups, respectively.

Amoxicillin-Clavulanic Acid showed a 84.8% efficacy against *E. coli* in patients aged below 16 and 87% in patients 16-35, while a 73.5% efficacy was found in patients above 75 years of age (Table 5).

Nitrofurantoin showed high levels of activity against *E. coli*, with approximately 97% sensitivity in patients aged above 75, while above this age it maintained a 92.4% efficacy.

DISCUSSION

Positive cultures were mostly from female patients (80%), in line with other studies.[7-9] *E. coli*, *Klebsiella pneumoniae* and *Proteus* were the three most common strains found in our study, also in line with other findings.[6,8-10] However, the *E. coli* prevalence (65.9%) was below what was estimated in the described studies, between 75 and 90%.[7] Patients aged above 75, corresponding to 34.5% of our sample, showed a decrease in the prevalence of this strain (55.4%). In-hospital patients had a lower *E. coli* prevalence (61.8%) than Out-patients (70.6%),[9] emphasizing the effect of institutionalisation on isolate prevalence.

Klebsiella pneumoniae was found in 12% of all urine cultures, corresponding to a higher prevalence than in the abovementioned studies, where it varied between 3.7%[6] and 10%.[8] We found a 16.3% prevalence in the age group above 75, again higher than what was described in other studies.

UTI empirical therapy should be based on the knowledge of major involved microbial agents and on their antimicrobial sensitivity profile.[11] *E. coli* showed high sensitivity percentage to Fosfomycin (96.6%) which, according to the Portuguese Health Directorate General,[12] allows for an efficient empirical use of this antibiotic. Sensitivity to quinolone, represented by Ciprofloxacin (78.4%) and Levofloxacin (75%), is in line with what was found in other studies,[6] being considered

Table 2 - Prevalence of bacterial strains per age group

	Age Group										Total	
	< 16		16 - 35		36 - 55		56 - 75		> 75			
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
E. coli	65	67.0	485	72.4	961	74.6	1,282	69.4	1,163	55.4	3,956	65.9
Klebsiella P.	7	7.2	63	9.4	110	8.5	197	10.7	342	16.3	719	12.0
P. mirabilis	21	21.6	43	6.4	62	4.8	123	6.7	172	8.2	421	7.0
Total	**93**	**95.9**	**513**	**88.2**	**1,133**	**88.0**	**1,454**	**86.8**	**1,677**	**79.9**	**4,470**	**84.9**

n = absolute frequency; % = relative frequency; *Klebsiella P. = Klebsiella pneumoniae; P. mirabilis = Proteus mirabilis.*

Table 3 - Antimicrobial sensitivity profile (%)

Antibiotic	*E. coli*	*Klebsiella*	*Proteus*	*E. faecalis*	*Pseudomonas*	*Morganella*
Amikacin	96.1	95.7	99.0	N/A	92.33	94.2
Ampicillin	62.5	20.4	68.5	79.3	N/A	1.0
Amox-ClavAc	81.1	71.1	87.7	4.8	40	1.5
Ceftazidime	91.8	72.0	90.9	N/A	79.7	71.4
Ciprofloxacin	78.4	65.4	66.5	N/A	57.1	39
Ceftriaxone	94.9	75.8	96.8	N/A	N/A	N/A
Cefuroxime	86.1	65.5	87.2	7.2	20.0	N/A
Co-trimoxazole	75.5	66.4	60.1	N/A	N/A	35.9
Fosfomycin	96.6	59.8	81.4	N/A	N/A	N/A
Gentamicin	93.0	76.9	85.4	N/A	86.5	59.0
Imipenem	99.9	99.5	36.6	76.3	73.2	32
Levofloxacin	75.0	75.0	N/A	N/A	N/A	N/A
Nitrofurantoin	96.0	N/A	N/A	96.0	N/A	N/A
Benzylpenicillin	N/A	N/A	N/A	74.5	N/A	N/A
Pip-Tazobactan	96.8	81.1	91.2	N/A	62.7	N/A

N/A: Not available; Pip: piperacillin.

Table 4 - *E. coli* sensitivity profile to Fosfomycin per age group

		Age Group										Total	
		< 16		16 - 35		36 - 55		56 - 75		> 75			
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Fosfomycin	**R**	0	0.0	5	1.5	11	1.6	23	2.6	55	6.6	94	3.4
	S	44	100.0	334	98.5	668	98.4	859	97.4	784	93.4	2,689	96.6
Total		44	100.0	339	100.0	679	100.0	882	100.0	839	100.0	2,783	100.0

R = Resistant; S = Sensitive; *n* = absolute frequency; % = relative frequency.

Table 5 - *E. coli* sensitivity profile to Amoxicillin-Clavulanic Acid per age group

		Age Group										Total	
		< 16		16 - 35		36 - 55		56 - 75		> 75			
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Amoxicillin-Clavulanic Acid	**R**	7	15.2	46	13.0	112	16.2	147	16.4	227	26.5	539	18.9
	S	39	84.8	309	87.0	581	83.8	751	83.6	628	73.5	2,308	81.1
Total		46	100	355	100	693	100	898	100	855	100	2,847	100

R = Resistant; S = Sensitive; *n* = absolute frequency; % = relative frequency.

as low, which may be explained by its excessive use and Portugal is among the countries with higher consumption of this medication.[3,15]

Klebsiella pneumoniae, which represented 12% of the isolated bacteria, shows a low percentage of sensitivity to the Amoxicillin-Clavulanic Acid (71.1%), Cefuroxime (65.5%) and Cotrimoxazole (66.6%), in line with a previous Portuguese study carried out in 2007.[9] This fact prevents empirical Out-patient therapy for infections related to this strain.

Proteus mirabilis only represented 7% of all the isolates although, from these, 21.6% were a cause for UTI in the age group below 16 years of age. It showed a low percentage of sensitivity to quinolone (Ciprofloxacin 65.4% and Levofloxacin 75%) and therefore these should not be a first-line therapeutic option. It only showed a high sensitivity to Imipenem (99.5%) and Amikacin (95.7%), two drugs not being available in an Out-patient setting. *Proteus mirabilis* is sensitive to Ceftriaxone in 96.8% of the samples.

Nitrofurantoin shows a high efficacy against *E. coli* (96%) and *E. faecalis* (96%), which may be related to having been disused over the last few years. The need for a long-term regimen (at least seven days), four times per day, associated to its toxicity, determines that it should be used carefully in an outpatient regimen.[7]

Amikacin showed a high sensitivity against the five major agents (*E. coli*, *Klebsiella*, *Proteus*, *Pseudomonas* and *Morganella*), corresponding to 90% of all the samples in our study.

Second-generation cephalosporin, represented by Cefuroxime, showed a lower efficacy against *E. coli* (86.1%) and *Proteus mirabilis* (87.2%), when compared to third-generation's (Ceftazidime and Ceftriaxone), which is above 90%.

The 15/2011 Portuguese guideline[12] recommends Nitrofurantoin, Fosfomycin or Amoxicillin-Clavulanic Acid in treatment of uncomplicated acute cystitis. The results of our study give support to these guidelines regarding Nitrofurantoin or Fosfomycin, both with efficacy against *E. coli*, the most prevalent bacteria found (66% of the samples). The same does not apply to the Amoxicillin-Clavulanic Acid, which shows a 84.8% and 87% sensitivity in patients aged below 16 and 16-35, respectively, dropping to 73.5% in patients aged above 75. Our study does not allow for definitive conclusions because it was based on the analysis of urine culture results alone and did not take into consideration the patient's clinical situation, the main limitation of our study. .

CONCLUSION

UTI empirical therapy should be based on consensual recommendations;[7-12] however, a knowledge of strain prevalence and antimicrobial sensitivity is required..

Most frequent bacterial strains involved in community-acquired UTI are *Escherichia coli* (65.9%), followed by *Klebsiella pneumoniae* (12%) and *Proteus mirabilis* (7%).

In all age groups, *Escherichia coli* strains demonstrate 93% sensitivity to Fosfomycin and 96% to Nitrofurantoin. As such, these therapies are recommended in uncomplicated acute cystitis in the female patients. However, they should be used with special care in patients aged above 75, in whom sensitivity prevalence is just 55.4%.

Amoxicillin-Clavulanic Acid, with lower efficacy against *E. coli* (81.1%), does not show any advantage when

compared to Fosfomycin.

E. coli strains show 78% sensitivity to quinolone, below Fosfomycin and Nitrofurantoin. We should also mention that both have no parenchymal penetration and therefore are not appropriated for upper urinary tract infections (pyelonephritis) or prostate infections.

Further similar studies are recommended in order to follow the evolution of microbial sensitivity profile and to optimize UTI empirical therapy.

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CONFLICTS OF INTEREST

The authors declare that there was no conflict of interests in writing this manuscript.

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