ANTIMICROBIAL SUSCEPTIBILITY PROFILE OF *Staphylococcus haemolyticus* ISOLATED FROM VIETNAMESE CANCER PATIENTS OVER 4 YEARS

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ABSTRACT

S. haemolyticus is frequently colonizing the hospital environment and resistance to multiple antibiotics. The antimicrobial-resistant data of S. haemolyticus from Vietnamese cancer patients are limited. This study aims to evaluate the antimicrobial susceptibility profile of 41 S. haemolyticus isolated from Vietnamese cancer patients over a period of 4 years.

The rate of methicillin-resistant and multidrug-resistant was 48.8% (20/41) and 95.1% (39/41), respectively. The most frequent sample was blood (65.9%, 27/41), and the second most frequent was sputum (12.2%, 5/41).

All isolates were susceptible to quinupristin-dalfopristin, linezolid, tigecycline, and nitrofurantoin, and about 97% of isolates were susceptible to vancomycin. Approximately 96.88% of isolates were resistant to Benzylpenicillin and oxacillin, 93.75% were resistant to erythromycin, and 90.63% were resistant to Ciprofloxacin and Levofloxacin. The high level of methicillin and multidrug-resistant and reduced susceptibility to many antibiotics are causes of concern since they further narrow down the therapeutic options.

Quinupristin-dalfopristin, linezolid, tigecycline, nitrofurantoin, and vancomycin are effective against S. haemolyticus infection in Vietnamese cancer patients at Vietnam National Cancer Hospital/Tan Trieu Base. Further studies are needed to surveillance bacterial resistance to guide antimicrobial therapy, reduce antimicrobial resistance rates, and improve the Vietnamese cancer patient's care.

***Keywords**: S. haemolyticus, MRSA, MDR, Vietnamese, cancer*

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1. INTRODUCTION

Staphylococci belong to the *Micrococcaceae* family. These bacteria are Gram-positive cocci and present in the mucosa, on the skin of humans, mammals, and birds. *Staphylococci* includes a total of 51 species and can be divided into two groups, e.g., coagulase-positive *Staphylococci* (e.g., *Staphylococcus aureus*) and coagulase-negative *Staphylococci* (CoNS), including *Staphylococcus haemolyticus*. The species that frequently cause human disease are *S. aureus*, *S. epidermidis*, and *S. haemolyticus*. These pathogens infections are most prevalent in the community and the hospital. The pathogens spread from person to person through direct contact or exposure to contaminated medical devices [1].

S. haemolyticus is one of the major species of CoNS. It is a major opportunistic pathogen-related nosocomial infection, especially in immunocompromised patients such as cancer patients. *S. haemolyticus* is an emerging opportunistic pathogen associated with hospital-acquired infections and with a high burden of antimicrobial resistance. *S. haemolyticus* is frequently colonizing the hospital environment and resistance to multiple antibiotics [2]. *S. haemolyticus* may cause various infections such as septicemia, peritonitis, urinary tract, and respiratory infections [3].

S. haemolyticus is the most common pathogen colonizing humans, medical materials, devices. They are also the main pathogens involved in bacteremia, accounting for 30% of bloodstream-associated infections, particularly in immunocompromised individuals, e.g. cancer patients [4].

The origin of CoNS-associated infections is in the hospital environment. The emergence of CoNS antimicrobial resistance leads to the limitation of treatment options, and that is a growing public health concern. Despite the huge antimicrobial-resistant data of *S. haemolyticus* published worldwide, the antimicrobial-resistant profile of *S. haemolyticus* from Vietnamese cancer patients remains largely unknown. Thus, the present study aims to evaluate the antimicrobial resistance profiles of *S. haemolyticus* isolated from Vietnamese cancer patients over a period of 4 years.

2. MATERIALS AND METHODS

Ethical considerations

Ethical approval for laboratory data was not required as the study was routine surveillance measures for infection control.

Isolates

The *S. haemolyticus* was isolated between 2020 and 2024 from various samples of Vietnamese cancer inpatients admitted to Vietnam National Cancer Hospital/Tan Trieu Base. Only one isolate per patient was collected.

Identification and antimicrobial susceptibility testing of *S. haemolyticus*

The samples were collected according to routine procedures of the Medical Microbiology Department. Bacteria isolates were identified by biochemical methods using an automated Vitek 2 compact system (BioMérieux).

The antibiotic susceptibility testing for isolated pathogens was performed using

and automated Vitek 2 compact system (BioMérieux). The antimicrobial susceptibility testing results were interpreted according to Clinical and Laboratory Standards Institute guidelines (2020). The multidrug-resistant pathogens were defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories.

Statistical analysis

R version 3.6.3 was used to analyze the data. The Chi-squared or Fisher's exact test evaluated associations between categorical variables. The student's T-test or the Mann-Whitney U test was used to assess associations between normalized and un-normalized continuous variables, respectively. A p-value of < 0.05 was considered statistically significant.

3. RESULTS

Clinical features

Table 3.1. Demographic, clinical and laboratory features of Vietnamese cancer patients in the present study

	Female (n = 9)	Male (n = 32)	Overall (n = 41)	P-value
Diagnostic				
Brain Tumor	1 (11.1%)	4 (12.5%)	5 (12.2%)	0.911
Breast cancer	3 (33.3%)	0 (0%)	3 (7.3%)	
Colorectal cancer	2 (22.2%)	3 (9.4%)	5 (12.2%)	
Lung cancer	1 (11.1%)	7 (21.9%)	8 (19.5%)	
Lymphomas	1 (11.1%)	3 (9.4%)	4 (9.8%)	
Renal cancer	1 (11.1%)	1 (3.1%)	2 (4.9%)	
Cholangiocarcinoma	0 (0%)	2 (6.3%)	2 (4.9%)	
Esophageal cancer	0 (0%)	3 (9.4%)	3 (7.3%)	
Gastric cancer	0 (0%)	1 (3.1%)	1 (2.4%)	
Hepatocellular carcinoma	0 (0%)	2 (6.3%)	2 (4.9%)	
Mediastinal tumor	0 (0%)	1 (3.1%)	1 (2.4%)	
Melanoma	0 (0%)	1 (3.1%)	1 (2.4%)	
Nasopharyngeal cancer	0 (0%)	2 (6.3%)	2 (4.9%)	
Spine tumor	0 (0%)	2 (6.3%)	2 (4.9%)	
Age				
Mean (SD)	52.4 (21.1)	61.5 (15.2)	59.5 (16.8)	0.456
Median [Min, Max]	53.0 [13.0, 77.0]	66.5 [17.0, 85.0]	64.0 [13.0, 85.0]	

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	Female (n = 9)	Male (n = 32)	Overall (n = 41)	P-value
Unit				
Department of Surgery	3 (33.3%)	2 (6.3%)	5 (12.2%)	0.388
Intensive care unit	4 (44.4%)	23 (71.9%)	27 (65.9%)	
Treatment on Demand	2 (22.2%)	4 (12.5%)	6 (14.6%)	
Internal Medicine	0 (0%)	3 (9.4%)	3 (7.3%)	
Sample				
Blood	7 (77.8%)	20 (62.5%)	27 (65.9%)	0.799
Cerebrospinal fluid	1 (11.1%)	1 (3.1%)	2 (4.9%)	
Pus	1 (11.1%)	0 (0%)	1 (2.4%)	
Catheter	0 (0%)	2 (6.3%)	2 (4.9%)	
Sputum	0 (0%)	5 (15.6%)	5 (12.2%)	
Urine	0 (0%)	2 (6.3%)	2 (4.9%)	
Wound fluid	0 (0%)	2 (6.3%)	2 (4.9%)	
Methicillin-resistant				
Negative	6 (66.7%)	15 (46.9%)	21 (51.2%)	0.577
Positive	3 (33.3%)	17 (53.1%)	20 (48.8%)	
D-test				
Missing	2 (22.2%)	3 (9.4%)	5 (12.2%)	0.849
Negative	6 (66.7%)	22 (68.8%)	28 (68.3%)	
Positive	1 (11.1%)	7 (21.9%)	8 (19.5%)	
Multidrug-resistant				
No	1 (11.1%)	1 (3.1%)	2 (4.9%)	0.617
Yes	8 (88.9%)	31 (96.9%)	39 (95.1%)	

The clinical features of Vietnamese cancer patients are shown in Table 3.1. A total of 41 *S. haemolyticus* were analyzed. Of the 41 *S. haemolyticus* isolates, 27 (66%) were from the blood, 5 (12%) from sputum, 2 (4.9%) from the catheter, cerebrospinal fluid, urine, and wound fluid and 1 (2.45%) from pus. Among 41 *S. haemolyticus* isolates, 27 (66%) were isolated from the Intensive Care Unit, 6 (15%) from the Department of Treatment on Demand, 5 (12%) from the Department of Surgery, 3 (7.3%) from Department of Internal Medicine.

Antimicrobial-resistant profile

Antibiotic susceptibility testing results and resistance of the *S. haemolyticus* isolates to antibiotics are shown in Table 3.2 (see below) and Figure 3.1, respectively.

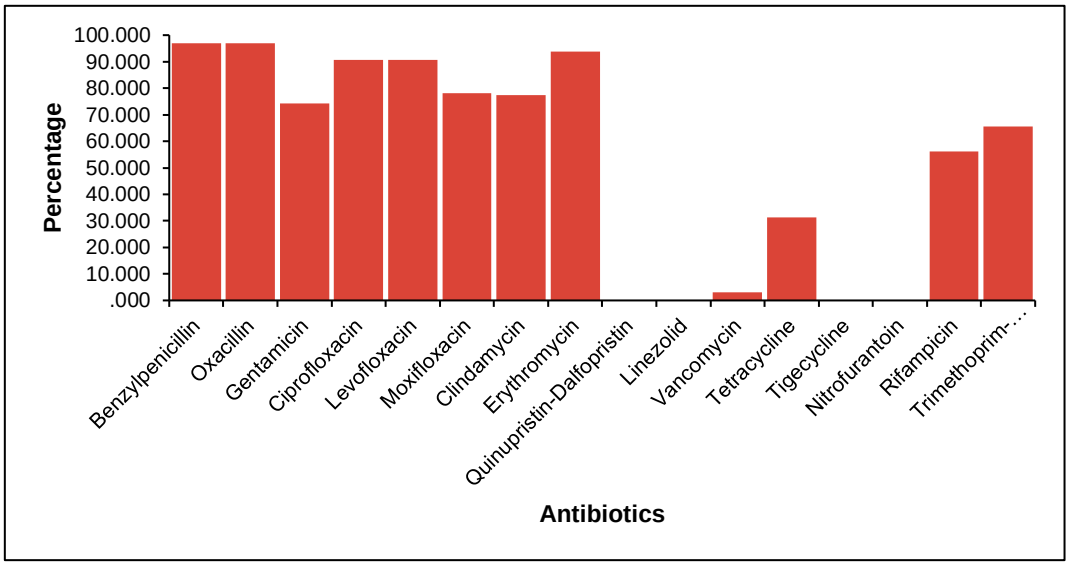

Figure 3.1. Antibiotic resistance pattern of *S. haemolyticus* in Vietnamese cancer patients

Table 3.2. The antimicrobial susceptibility testing result of *S. haemolyticus* in Vietnamese cancer patients

Antimicrobial	N	Overall (N = 41)	95% CI[1]	MRSA				
				Negative (N = 21)	95% CI[1]	Positive (N = 20)	95% CI[1]	p-value
Benzylpenicillin, n (%)	40							> 0.99[2]
R		39/40 (97.50%)	85%, 100%	19/40 (47.50%)	73%, 100%	20/40 (50.00%)	80%, 100%	
S		1/40 (2.50%)	0.13%, 15%	1/40 (2.50%)	0.26%, 27%	0/40 (0.00%)	0.00%, 20%	
Missing		1		1		0		
Oxacillin, n (%)	40							> 0.99[2]
R		39/40 (97.50%)	85%, 100%	19/40 (47.50%)	73%, 100%	20/40 (50.00%)	80%, 100%	
S		1/40 (2.50%)	0.13%, 15%	1/40 (2.50%)	0.26%, 27%	0/40 (0.00%)	0.00%, 20%	
Missing		1		1		0		

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Antimicrobial	N	Overall (N = 41)	95% CI[1]	MRSA				
				Negative (N = 21)	95% CI[1]	Positive (N = 20)	95% CI[1]	p-value
Gentamicin, n (%)	39							0.672
R		28/39 (71.79%)	55%, 84%	13/39 (33.33%)	43%, 86%	15/39 (38.46%)	51%, 90%	
S		8/39 (20.51%)	9.9%, 37%	5/39 (12.82%)	10%, 51%	3/39 (7.69%)	4.0%, 39%	
I		3/39 (7.69%)	2.0%, 22%	1/39 (2.56%)	0.28%, 28%	2/39 (5.13%)	1.8%, 33%	
Missing		2		2		0		
Ciprofloxacin, n (%)	40							> 0.99[2]
R		34/40 (85.00%)	69%, 94%	17/40 (42.50%)	61%, 96%	17/40 (42.50%)	61%, 96%	
S		5/40 (12.50%)	4.7%, 28%	3/40 (7.50%)	4.0%, 39%	2/40 (5.00%)	1.8%, 33%	
I		1/40 (2.50%)	0.13%, 15%	0/40 (0.00%)	0.00%, 20%	1/40 (2.50%)	0.26%, 27%	
Missing		1		1		0		
Levofloxacin, n (%)	40							> 0.99[2]
R		34/40 (85.00%)	69%, 94%	17/40 (42.50%)	61%, 96%	17/40 (42.50%)	61%, 96%	
S		6/40 (15.00%)	6.2%, 31%	3/40 (7.50%)	4.0%, 39%	3/40 (7.50%)	4.0%, 39%	
Missing		1		1		0		
Moxifloxacin, n (%)	40							> 0.99[2]
R		30/40 (75.00%)	58%, 87%	15/40 (37.50%)	51%, 90%	15/40 (37.50%)	51%, 90%	
S		6/40 (15.00%)	6.2%, 31%	3/40 (7.50%)	4.0%, 39%	3/40 (7.50%)	4.0%, 39%	
I		4/40 (10.00%)	3.3%, 25%	2/40 (5.00%)	1.8%, 33%	2/40 (5.00%)	1.8%, 33%	
Missing		1		1		0		
Clindamycin, n (%)	39							>

Antimicrobial	N	Overall (N = 41)	95% CI[1]	MRSA				
				Negative (N = 21)	95% CI[1]	Positive (N = 20)	95% CI[1]	p-value
								0.99[2]
R		31/39 (79.49%)	63%, 90%	15/39 (38.46%)	54%, 93%	16/39 (41.03%)	56%, 93%	
S		7/39 (17.95%)	8.1%, 34%	4/39 (10.26%)	7.0%, 46%	3/39 (7.69%)	4.0%, 39%	
I		1/39 (2.56%)	0.13%, 15%	0/39 (0.00%)	0.00%, 21%	1/39 (2.56%)	0.26%, 27%	
Missing		2		2		0		
Erythromycin, n (%)	40							0.492
R		38/40 (95.00%)	82%, 99%	18/40 (45.00%)	67%, 98%	20/40 (50.00%)	80%, 100%	
S		2/40 (5.00%)	0.87%, 18%	2/40 (5.00%)	1.8%, 33%	0/40 (0.00%)	0.00%, 20%	
Missing		1		1		0		
Quinupristin-Dalfopristin, n (%)	40							
S		40/40 (100.00%)	89%, 100%	20/40 (50.00%)	80%, 100%	20/40 (50.00%)	80%, 100%	
Missing		1		1		0		
Linezolid, n (%)	39							> 0.99[2]
S		38/39 (97.44%)	85%, 100%	19/39 (48.72%)	73%, 100%	19/39 (48.72%)	79%, 100%	
R		1/39 (2.56%)	0.13%, 15%	1/39 (2.56%)	0.26%, 27%	0/39 (0.00%)	0.00%, 21%	
Missing		2		1		1		
Vancomycin, n (%)	40							> 0.99[2]
S		39/40 (97.50%)	85%, 100%	20/40 (50.00%)	80%, 100%	19/40 (47.50%)	73%, 100%	
R		1/40 (2.50%)	0.13%, 15%	0/40 (0.00%)	0.00%, 20%	1/40 (2.50%)	0.26%, 27%	
Missing		1		1		0		
Tetracycline, n (%)	40							0.513

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Antimicrobial	N	Overall (N = 41)	95% CI[1]	MRSA				
				Negative (N = 21)	95% CI[1]	Positive (N = 20)	95% CI[1]	p-value
S		26/40 (65.00%)	48%, 79%	14/40 (35.00%)	46%, 87%	12/40 (30.00%)	36%, 80%	
R		14/40 (35.00%)	21%, 52%	6/40 (15.00%)	13%, 54%	8/40 (20.00%)	20%, 64%	
Missing		1		1		0		
Tigecycline, n (%)	36							
S		36/36 (100.00%)	88%, 100%	20/36 (55.56%)	80%, 100%	16/36 (44.44%)	76%, 100%	
Missing		5		1		4		
Nitrofurantoin, n (%)	40							
S		40/40 (100.00%)	89%, 100%	20/40 (50.00%)	80%, 100%	20/40 (50.00%)	80%, 100%	
Missing		1		1		0		
Rifampicin, n (%)	40							0.753
R		23/40 (57.50%)	41%, 73%	11/40 (27.50%)	32%, 76%	12/40 (30.00%)	36%, 80%	
S		17/40 (42.50%)	27%, 59%	9/40 (22.50%)	24%, 68%	8/40 (20.00%)	20%, 64%	
Missing		1		1		0		
Trimethoprim-Sulfamethoxazole, n (%)	40							0.743
R		27/40 (67.50%)	51%, 81%	14/40 (35.00%)	46%, 87%	13/40 (32.50%)	41%, 84%	
S		13/40 (32.50%)	19%, 49%	6/40 (15.00%)	13%, 54%	7/40 (17.50%)	16%, 59%	
Missing		1		1		0		

[1]CI = Confidence Interval, [2]Fisher's exact test, [3]Pearson's Chi-squared test

All isolates of *S. haemolyticus* were sensitive to quinupristin-dalfopristin, linezolid, tigecycline, and nitrofurantoin.

Only 3.13% (1/41) of the *S. haemolyticus* isolates resistant to vancomycin while 96.88% of *S. haemolyticus* isolates were resistant to benzylpenicillin and oxacillin, 93.75% of *S. haemolyticus* isolates were resistant to erythromycin, 90.63% of *S. haemolyticus*

isolates were resistant to ciprofloxacin and levofloxacin.

The average multidrug-resistant was 95.1% (39/41) in all *S. haemolyticus* isolates. The average resistance to methicillin was 48.8% (20/41).

4. DISCUSSION

In the present study, the most common *S. haemolyticus* isolates were from blood (66%), which is much higher than other samples. The results indicate that among CoNS, *S. haemolyticus* isolates are responsible for a significant number of bloodstream infections in Vietnamese cancer patients. This finding is consistent with previous reports [5].

Antibiotic resistance is a public health concern all over the world. Antibiotic resistance pathogens are emerging from different countries [6]. We found that the average multidrug-resistant was 95.1% in all *S. haemolyticus* isolates, much higher than previously reported that about 70% of clinical and commensal *S. haemolyticus* strains were multidrug-resistant [4]. *S. haemolyticus* has a great potential of developing multidrug-resistant. The high multidrug-resistant rate highlights *S. haemolyticus* as a multidrug-resistant pathogen that is difficult to treat with conventional antibiotics.

In the present study, the average resistance to methicillin was high (48.8%, 20/41). The methicillin-resistant implications for a worse prognosis and increased demand for healthcare resources. Patients infected with methicillin-resistant *S. haemolyticus* require a greater cost and are associated with prolonged hospital stays and higher mortality. Thus, the identification of colonized individuals to reduce the risk of acquiring a methicillin-resistant infection is needed [1].

CoNS-related human infection resistance to antimicrobials is increasingly common, especially resistance to oxacillin and/or methicillin [4]. Methicillin-resistant *Staphylococci* are a global health concern. In the present study, the resistance rates of *S. haemolyticus* to oxacillin and benzylpenicillin were 96.88% which is much higher than that in other reports that the prevalence of CoNS methicillin resistance rate ranged from 70% to 80%, whereas oxacillin resistance rate ranged from 75 - 85% in recent years [4], and that is a growing concern.

The resistance rates of CoNS to linezolid range from 1% to 2% [7]. However, the isolates in the present study were 100% susceptible to linezolid, which is consistence with other reported [4]. The frequent use of linezolid is associated with resistance, mainly involving cases of clonal dissemination. Linezolid is an oxazolidinone antibiotic, with activity against Gram-positive pathogens including MRSA. The unique linezolid-resistant mechanism involves the inhibition of bacterial protein synthesis through the 23 Sr RNA gene. Resistance to linezolid is an infrequent phenomenon [8]. Our results showed that linezolid remains one of the most effective antibiotics against *S. haemolyticus*.

Tigecycline is a glycylcycline molecule and derivative of the tetracycline minocycline. Tigecycline has a great potent activity against tetracycline-resistant pathogens. Resistant clinical isolates were associated with efflux pumps [8]. Tigecycline is effective in the treatment of

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S. haemolyticus infections [4]. Accordingly, in the present study, all isolates are sensitive to tigecycline.

All of our isolates are susceptible to quinupristin-dalfopristin. Another study reported that they detected one (1.2%) isolate that was resistant to quinupristin-dalfopristin [4]. The quinupristin-dalfopristin is a combination of two semisynthetic agents quinupristin and dalfopristin, in a 30:70 ratio. The mechanisms of resistance to quinupristin-dalfopristin were increasing enzymatic modification, active transport of specific efflux pumps, and alteration of the target site. Resistance is rare in *Streptococci* and *Enterococcus faecium* species. Quinupristin-dalfopristin has good efficacy and the possibility of developing resistance to quinupristin-dalfopristin is low due to its prolonged post-antibiotic effect. Most CoNS strains are highly susceptible to daptomycin, and quinupristin-dalfopristin [8]. This study results showed that quinupristin-dalfopristin is effective in the treatment of *S. haemolyticus* infections.

All *S. haemolyticus* are susceptible to nitrofurantoin, the nitrofurantoin resistance is uncommon among CoNS. Thus, nitrofurantoin shows high efficacy against *S. haemolyticus* infections.

The present study results showed the efficacy of vancomycin against *S. haemolyticus*. We detected one (3.13%) isolate that was resistant to vancomycin. Vancomycin-resistant *S. haemolyticus* has emerged as an increasingly problematic cause of hospital-acquired infections and spreading into the community. The MIC values of vancomycin for *Staphylococcus* spp. are increasing worldwide [8].

The CoNS-reduced susceptibility to vancomycin has been increasing, posing the need for novel antimicrobials to solve the CoNS resistance concern. *S. haemolyticus* resistant to vancomycin is a matter of concern and CoNS were the first pathogens resistant to glycopeptide. The resistant MICs of vancomycin have increased progressively in recent years (more than 2 mg/ml was observed in a large number of *S. haemolyticus*). These results may indicate a decrease the efficacy (in vivo) of Vancomycin [4].

The rates of resistance to many antibiotics and the reduction in sensitivity to vancomycin steadily increasing posed the needed for the new drugs to treat CoNS infections. In this study, antibiotics such as quinupristin-dalfopristin, linezolid, tigecycline, nitrofurantoin, and vancomycin show excellent in vitro activity against *S. haemolyticus,* which is consistence with previously reported [8].

5. CONCLUSION

S. haemolyticus are important pathogen causing infections in Vietnamese cancer patients. The high level of methicillin and multidrug-resistant and reducing susceptibility to many antibiotics, e.g., benzylpenicillin and oxacillin, erythromycin, ciprofloxacin, and levofloxacin are causes of concern since they further narrow down the therapeutic options in Vietnamese cancer patients. However, antibiotics such as quinupristin-dalfopristin, linezolid, tigecycline, nitrofurantoin, and vancomycin are effective against *S. haemolyticus* infection in Vietnamese cancer patients at Vietnam National Cancer Hospital/Tan Trieu Base. Ongoing surveillance of antimicrobial resistance of *S. haemolyticus* is needed to understand emerging patterns of resistance,

which is important for hospital biosecurity and guiding treatment decisions.

Disclosure Statement

No competing financial interests exist.

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