

Resistance Pattern of Antibiotics in Patient Underwent Open Heart Surgery with Nosocomial Infection in North of Iran

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Abstract

Background: Patients who undergo cardiac surgery appear to be at increased risk for the development of Nosocomial infections (NIs). The development of antibiotic-resistant infections has been associated with significantly greater hospital mortality rates compared to similar infections caused by antibiotic-sensitive pathogens.

Objectives: The purpose of this study is survey of Nis and antibiotic resistance patterns of causative bacteria among patients who underwent open heart surgery in the north of Iran during a 2-year period between September 2012 and September 2014.

Methods: In this cross-sectional study we evaluated 187 patients that underwent open heart surgery with NIs. Demographic feature, clinical characteristics and risk factors of each infection were recorded. The antibiotic susceptibility test was performed using the Minimum inhibitory concentration (MIC) method according to the standard protocol of Clinical & Laboratory Standards Institute (CLSI). Detection of Extended-spectrum beta-lactamase (ESBL) producing bacteria was performed by the double-disk synergy (DDS) test; also Methicillin-resistant Staphylococcus (MRSA) strains were identified by MRSA Screen Agar. The collected data were analyzed using the SPSS software (ver. 16) and, descriptive statistics were used.

Results: Out Of total of 2253 hospitalized patients who underwent open heart surgery, 187(5.05%) patients had NIs. 51.9% of the patients were female. The rates of surgical site infection (SSI), respiratory tract infection, endocarditis, Urinary tract infection (UTI), blood Infection and mediastinitis were 27.80, 25.66%, 17.64, 17.11% 8.55% and 3.20% respectively. *E.coli* and *S.aureus* were the most causative agents of NIs. The rate of ESBL-producing bacteria was 14.28- 71.42% among enterobacteriaceae and the rate of MRSA was 54.2% among *S.aureus* strains. All isolated *Acinetobacter.spp* were Multi-drug resistance (MDR).

Conclusions: We showed that the rate of NIs among these high-risk patients was in the average level. But the emergence of MRSA and ESBL bacteria is increasing in our region.

Keywords: nosocomial infection, antibiotic resistance, open heart surgery, ESBL, MRSA

1. Introduction

Nosocomial infections (NIs) pose a serious threat to patients, especially in the high-risk wards (Ding et al., 2009). Globally, 8.7 % of the hospitalized patients are affected with NIs (Behzadnia et al., 2014). NIs after open heart surgery represent serious complications corresponding with significant morbidity, mortality, increased need for antimicrobial therapy and economic burden (Lola et al., 2011). NIs have been reported to occur in 5–21% of cardiac surgery patients and in these patients, infections are serious and often life-threatening complications (Kollef et al., 1997; Michalopoulos et al., 2006). Patients who undergo cardiac surgery appear to be at increased

risk for the development of NIs due to the presence of multiple surgical wounds, frequent postoperative utilization of invasive devices, and the common use of antibiotics in the perioperative period. Additionally, current administration practices of antibiotics may help to explain the emergence of NIs due to antibiotic resistant pathogens in this and other groups of critically ill patients. The development of such antibiotic-resistant infections has been associated with significantly greater hospital mortality rates compared to similar infections caused by antibiotic sensitive pathogens. Common problem in the treatment of NIs is the increase of antibiotic-resistant organisms (Kollef et al., 1995; Goldmann et al., 1996; Rahmati et al., 2014). Prevention of NIs remains of the uttermost importance. Identifying NIs risk factors and antibiotic resistance pattern of causative agents which vary between populations, is important in preventing infection in any patient who underwent open heart surgery. To the best of our knowledge this study is the first surveillance on patients that underwent open heart surgery with NIs in the north of Iran. The purpose of this study is survey of NIs and antibiotic resistance patterns of causative bacteria among patients who underwent open heart surgery in the Fatemeh Zahra teaching hospital to help the physicians choose better antibiotics in the start of empiric therapy.

2. Material and Methods

2.1 Study Population and Design

This is a cross-sectional study. This study was approved by the Ethics Committee of Mazandaran University of Medical Sciences (Code No: 9135, Date: July 11, 2012). All the patients with NIs who were admitted to Fatemeh Zahra teaching hospital (a governmental heart surgery center in Mazandaran province, northern Iran) in the period between September 2012 and September 2014 were studied. All these patients underwent open heart surgery. The census method was used for sampling. NIs were defined based on the National Directory of Nosocomial Infections Surveillance System (Masoumi, 2007). We gathered information that included demographic and clinical characteristics, risk factors, and medical history, and main diagnosis, types of NIs and clinical samples of the patients that had NIs.

2.2 Clinical Sample Collection and Identification of Bacteria

Samples included deep tissue infected through the wounds of surgical sites, sputum, tracheal secretions, wound debridement of infected tissue, drainage of mediastinum infected tissues, urine and blood. Sampling was done by the head nurse and the samples were immediately transported in a transport medium to the hospital's microbiology laboratory (To prevent the loss of some of the microorganisms present in the samples that take some time to culture and stain in the laboratory; we used Stuart transport medium). Identification of the organisms causing infection was performed according to the standard microbiological procedures (Koneman et al., 1997; Collee et al., 1996).

2.3 Antimicrobial Susceptibility Test

Susceptibility of the clinical isolates to routinely used antibiotics was determined by the standard broth dilution (micro dilution broth) technique. MIC is defined as the lowest concentration of an antibiotic that inhibits the visible growth of bacteria after overnight culture. The bacterial suspension equivalent to 0.5 McFarland standards was prepared provided in Müller-Hinton Broth (MHB) (Merck, Germany). The final standard concentration of the bacteria was increased to 5×10^5 CFU/ml. Serial concentrations of antibiotics were prepared from 512 μ g/ml to 1 μ g/ml. MIC was determined according to the recommendations of the standard protocol of CLSI (CLSI, 2010). The antibiotics that were used were Ceftriaxone, Ciprofloxacin, Gentamicin, Clindamycin, Oxacillin, Penicillin, Cotrimoxazole, Ampicillin, Vancomycin, Amikacin, Ceftazidime, Imipenem, Norfloxacin, Cefazolin and Novobiocin. The antibiotics were purchased from Sigma chemical company.

2.3.1 Detection of Extended-Spectrum Beta-Lactamase (ESBL) Producing Enterobacteriaceae

ESBL-producing enterobacteriaceae was detected using the double-disk synergy (DDS) test (Ramazanzadeh, 2010, Jarlier et al., 1988). ESBL presence was assayed using the following antibiotic disks (MAST, UK): cefotaxime (30 μ g), cefotaxime/clavulanic acid (30/10 μ g), ceftazidime (30 μ g), and ceftazidime/clavulanic acid (30/10 μ g). *Escherichia coli* ATCC 25922 strains served as positive control.

2.3.2 Detection of Methicillin-Resistant Staphylococcus (MRSA) Strains

For detection of methicillin-resistant Staphylococcus strains, Oxacillin Screen Agar (originally named MRSA Screen Agar) was used. Staphylococcus strains were cultured on Muller Hinton agar containing 4% NaCl and 6 mg/L oxacillin and were incubated for 24 hours.

2.4 Statistical Analysis

The collected data were analyzed using SPSS software (ver. 16). Descriptive statistics were used.

3. Results

Out of total of 2253 hospitalized patients with open heart surgery in the north of Iran during the 2-year period between September 2012 and September 2014, 187(5.05%) had NIs from which 90(48%) were female and 97(51.9%) were male. The average age was 63.45 ± 14.14 years old. The average duration of hospitalization was 7.32 ± 3.42 days.

The prevalence of surgical site infection (SSI), respiratory tract infection, endocarditis, urinary tract infection (UTI), blood Infection and mediastinitis were 27.80%, 25.66%, 17.64%, 17.11%, 8.55% and 3.20% respectively.

The demographic feature, risk factors and clinical characteristics of every infection have been demonstrated in table 1 and 2; the incidence causative agent of NIs are portrayed in table 3 and antibiotic resistance pattern of the bacteria that cause NIs are given in tables 4 and 5 .

The prevalence of ESBL bacteria for *P. aeruginosa*, *Acinetobacter*.spp, *E.coli*, *Enterobacter* .spp and *Klebsiella* .spp were 4(33.3%), 5(71.42%), 8(27.58%), 2(25%) and 1(14.28%) respectively. The rates of MRSA Staphylococcus strains for *S.aureus* and *S. epidermidis* were 26(54.2%) and 2(100%).

Table 1. Demographic feature and risk factors of infection

		Respiratory tract Infection No. (%)	SSI No. (%)	UTI No. (%)	Blood Infection No. (%)	Mediastinitis No. (%)	Endocarditis No. (%)	Total No. (%)
Gender	Female	22(45.5)	22(42.3)	22(68.78)	8(50)	1(16.7)	16(48.5)	90(48.)
	Male	26(54.5)	30(57.7)	10(31.25)	8(50)	5(83.3)	17(51.5)	97(51.9)
Age	Year	63.75±13.81	65±9.2	68±12.68	67.7±16.25	57±4.18	55.96±18.12	63.45±14.14
Average duration of hospitalization	Day	7.1±2.2	6.2±1.7	7.1±5.23	6.93±1.65	8.5±3.67	8.15±6.2	7.32±3.42
Risk factor	Diabetes	15(34.1)	26(50)	8(25)	9(56.3)	6(100)	11(33.3)	83(44.4)
	HTN	24(54.5)	29(55.8)	19(59.37)	10(62.5)	4(66.7)	8(24.2)	94(50.3)
	Cardiovascular disease	21(31.7)	22(42.3)	11(34.37)	8(50)	4(66.7)	5(15.2)	71(38)
	Urine catheter	13(27.8)	13(25)	23(71.87)	7(43.8)	6(100)	9(27.3)	101(54)
	Central venous device	0	0	0	0	3(50)	2(6.06)	5(2.67)
	Mechanical intubation	41(93.2)	12(23.1)	13(40.62)	5(31.3)	6(100)	8(24.2)	85(45.5)
	Steroid therapy	1(2.3)	0	3(9.37)	0	0	4(12.1)	8(4.3)
	Lung diseases	5(11.4)	11(21.2)	6(18.75)	0	0	2(6.1)	24(12.7)
	Liver Cirrhosis	2(4.5)	0	2(6.25)	0	0	0	4(2.1)
	Renal failure	6(13.6)	1(1.9)	5(15.62)	3(18.8)	0	2(6.1)	17(9.1)
	Malignancy	0	0	0	0	0	0	0
	Chemotherapy	0	0	0	0	0	0	0
Transplantation	0	0	3(1.6)	0	0	0	3(1.6)	

Table 2. Clinical characteristics of infection

		Respiratory tract Infection	SSI No. (%)	UTI No. (%)	Blood Infection No. (%)	Mediastinitis	Endocarditis	Total No. (%)
Symptoms	Fever	35(79.5)	13(25)	24(75)	15(93.8)	4(66.7)	5(15.2)	96(51.3)
	Dysuria	0	0	16(8.6)	0	0	0	16(8.6)
	Frequent urination	0	0	16(8.6)	0	0	0	16(8.6)
	Flank pain	0	0	4(2.1)	0	0	0	4(2.1)
	Suprapubic pain	0	0	3(1.6)	0	0	0	3(1.6)
	Nausea	0	0	0	0	0	1(.3)	1(.3)
	Vomiting	0	0	0	0	0	1(.3)	1(.3)
	Chest pain	5(11.4)	1(1.9)	0	1(6.3)	0	1(.3)	8(4.3)
	Cough	9(20.5)	0	0	0	0	1(.3)	10(5.3)
	Increase of sputum	39(88.6)	0	3(1.6)	0	6(100)	0	48(25.7)
	Dyspnea	32(72.7)	1(1.9)	6(3.2)	4(25)	4(66.7)	1(.3)	48(25.7)
	Wound erythema	0	40(76.92)	0	0	4(66.7)	0	44(23.4)
	Wound oozing	0	39(75)	1(3.12)	0	4(66.7)	0	44(23.4)
	Suture openings	0	16(30)	0	0	0	0	16(8.6)

Table 3. Causative agent of NIs

Causative agent by site	No.(%) episodes of infection						
	SSI NO (%)	Respiratory Infection NO (%)	UTI NO (%)	Blood Infection NO (%)	Mediastinitis NO (%)	Endocarditis NO (%)	Total (N=187) NO (%)
	52(27.8)	48(25.6)	32(17.1)	16(8.55)	6(3.2)	33(17.6)	
<i>P. aeruginosa</i>	2(3.84)	8(16.66)	2(6.25)	0	0	0	12(13.79%)
<i>Acinetobacter.spp</i>	1(1.92)	3(6.25)	1(3.12)	0	1(16.6)	1(3.03)	7(8.04%)
<i>E.coli</i>	7(13.46)	6(12.5)	16(50)	0	0	0	29(33.33%)
<i>Enterobacter .spp</i>	3(5.76)	2(4.16)	3(9.37)	0	0	0	8(9.19%)
<i>Klebsiella.spp</i>	3(5.76)	0	3(9.37)	1(6.25)	0	0	7(8.04%)
<i>S. aureus</i>	14(26.92)	5(10.41)	0	6(37.5)	3(18.75)	5(9.09)	33(37.93%)
<i>S. epidermidis</i>	1(1.92)	0	1(3.12)	0	0	0	2(2.29%)
Enterococci	0	0	0	0	0	1(3.03)	1(1.14%)
Culture negative	21(4.3)	20(41.66)	6(18.75)	9(56.25)	2(33.33)	26(78.78)	88(47.1%)

Table 4. Antibiotic resistance pattern of gram negative bacteria isolated from infection

Antibiotics	<i>Pauroginosa</i>			<i>Acinetobacter.spp</i>			<i>E.coli</i>			<i>Enterobacter .spp</i>			<i>Klebsiella.spp</i>		
	NO.(%)			NO.(%)			NO.(%)			NO.(%)			NO.(%)		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Ceftriaxone	0	10	2	0	0	7	3	24	2	4	3	1	0	3	4
		(83.3)	(16.6)			(100)	(10.3)	(82.75)	(6.89)	(50)	(37.5)	(12.5)		(37.5)	(57.1)
Ceftazidime	2	4	6	0	0	7	3	18	8	0	3	5	1	1	5
	(16.6)	(33.3)	(50)			(100)	(10.3)	(62.06)	(27.5)		(37.5)	(62.5)	(14.2)	(14.2)	(71.42)
Ciprofloxacin	2	8	2	0	0	7	3	24	2	3	3	2	1	2	4
	(16.6)	(66.6)	(16.6)			(100)	(10.3)	(82.7)	(6.89)	(37.5)	(37.5)	(25)	(14.2)	(28.5)	(57.1)
Gentamicin	10	0	2	0	0	7	25	2	2	3	2	3	3	1	3
	(83.3)		(16.6)			(100)	(86.2)	(6.89)	(6.89)	(37.5)	(25)	(37.5)	(37.5)	(14.2)	(42.85)
Amikacin	10	2	0	0	0	7	27	0	2	3	2	3	4	0	3
	(83.3)	(16.6)				(100)	(93.1)		(6.89)	(37.5)	(25)	(37.5)	(57.1)		(42.85)
Imipenem	10	0	2	0	0	7	23	2	4	2	1	5	3	1	3
	(83.3)		(16.6)			(100)	(79.3)	(6.89)	(13.8)	(25)	(12.5)	(62.5)	(37.5)	(14.2)	(42.85)
Novobiocin	0	10	2	0	0	7	8	19	2	1	2	5	3	2	2
		(83.3)	(16.6)			(100)	(27.58)	(65.51)	(6.89)	(12.5)	(25)	(62.5)	(42.85)	(28.5)	(28.5)

Table 5. Antibiotic resistance of gram positive bacteria isolated from infection

	<i>S.aureus</i> NO			<i>S.epidermidis</i> NO		
	NO (%)			NO (%)		
	S	I	R	S	I	R
Ampicillin	4(12.9)	15(48.38)	12(38.70)	0	2(100)	0
Penicillin	0	19(61.29)	12(38.70)	0	2(100)	0
Oxacillin	2(6.45)	3(9.67)	26(83.87)	0	0	2(100)
Vancomycin	30(96.77)	0	1(3.22)	2(100)	0	0
Clindamycin	0	19(61.29)	12(38.70)	2(100)	0	0
Co-trimoxazole	0	19(61.29)	12(38.70)	0	0	2(100)
Norfloxacin	7(22.58)	12(38.70)	19(61.29)	2(100)	0	0
Cefalotin	17	7(22.58)	7(22.58)	0	2(100)	0

4. Discussions

Despite advances in antisepsis, asepsis, antibiotic prophylaxis and in surgical techniques, NIs continue to complicate after surgery in many patients (Segers et al., 2006). The rate of NIs in our study was 8.3%. Lomstadze et al. and Levy et al. reported the incidence of NIs in about 16% of patients that underwent heart surgery (Segers et al., 2006; Lee et al., 2010). However the rate of NIs in Sarvikivi et al study was 25 % (Sarvikivi et al., 2007). The rate of NIs after heart surgery in the study of Kollef, Sharpless et al. conducted in 1997 was 5-21% (Kollef et al., 1997). Michalopoulos and colleagues reported that 5% of patients developed microbiologically documented NIs after open cardiac surgery which is close to our findings (Michalopoulos et al., 2006).

SSI accounts for 15% of all NIs among surgical patients (Lee et al., 2010). SSI was diagnosed in 3% of the patients in Lepelletier et al study but in 13.5% in Lee et al study that was performed in Taiwan (Lee et al., 2010; Lepelletier et al., 2005). The most causative agent of SSI was *S.aureus* in our study. Similarly, this agent was the most common organism isolated in Mundhada et al. research (Mundhada & Tenpe, 2015). Lemaigen et al.

reported 4.1% occurrence of SSIs after cardiac surgery and, *S.aureus* was the most prevalent microorganism associated with them (Lemaigen et al., 2015). Risk factors for SSI were older age and diabetes in our study. Diabetes is one of the risk factors for the development of postoperative Nis in surgical patients. Patients with diabetes are more susceptible to many types of infection, including NIs and this has been the findings of Yamashita et al and Vardakas et al. (Yamashita et al., 2000; Vardakas et al., 2007). We observed that 4.3% of SSI was negative culture. The appearance of postoperative SSI in the absence of cultivable bacterial pathogens is a usual dilemma for the surgeons. Culture-negative SSIs happen because of prior antimicrobial therapies, the presence of fastidious or slow-growing bacteria such as *Legionella* spp, mycobacteria and *Mycoplasma* spp and infections caused by mundane bacteria that may be dismissed as contaminants, etc. (Rasnake & Dooley, 2006; Reddy, 2012).

Riera et al in Spain showed the rate of nosocomial pneumonia was 1.2% and the main risk factors for respiratory tract infections were left ventricular ejection fraction (Riera et al., 2010). Lomtadze et al in Georgia reported that the rate of nosocomial respiratory tract infections was 7% after heart surgery. Consistent with our results, Mechanical ventilation was one of the most common risk factors in Lomtadze et al study (Lomtadze et al., 2010; Lemaigen et al., 2015). *P. aeruginosa* and *S. aureus* were the most found bacteria isolated in pneumonia. In NIs pneumonia, *P. aeruginosa*, *A. baumannii*, and the Enterobacteriaceae are the main bacteria (Anton et al., 2010). We showed that 41.66% of pneumonia patients had negative culture results. Negative upper airway swab, alternative sampling methods such as induced sputum or broncho alveolar lavage may cause negative culture in NIs pneumonia (Ahmed et al., 2014).

Nosocomial endocarditis is associated with total parenteral nutrition lines, presence of intravenous catheters, pacemakers, etc. (Kasper & Harrison, 2005). In our study, 24.4% of the patients with nosocomial endocarditis had mechanical intubation and most causative bacteria were *S. aureus*. *Enterococci* and *Streptococcus bovis* were the most frequent bacteria in Barrau et al study (Barrau et al., 2004). Close to our findings, Takayama found *S. aureus* was responsible for endocarditis in 21.3% of the cases (Takayama et al., 2010). Close to 80% of endocarditis were negative culture, because some germs do not grow well in a laboratory setting and some people have taken antibiotics in the past that keep germs from growing.

The rate of UTI was 17.1% in our study and the main risk factor was urine catheter that was used on our patients. In a study that was conducted by Sodano et al in Italy, the rates of catheter-associated and device-associated UTIs in heart surgery patients were 5.8% and 6% respectively (Sodano et al., 2004). Also Mirinazhad et al. in Iran showed that all the patients had NIs associated with positive urine culture related to catheter-associated UTI. The most common microorganisms that Mirinazhad et al isolated were *Enterobacter* spp. (37.5%) (Mirinazhad et al., 2011). However *E.coli* was the most common bacteria isolated in our study. According to many studies in Iran, the main cause of UTI is still *E. coli* (Aminizadeh & Kashi, 2011; Behzadnia et al., 2014; Rezai et al., 2015; Saffar et al., 2008; Davoudi et al., 2012). In our study, 18.7% of the patients with UTI had negative culture.

Lomtadze et al. found the rate of blood infection to be 7.75% which is consistent with our results (Lomtadze et al., 2010). Barker reported 0.3% mediastinitis and 0.09% endocarditis in pediatric patients after cardiac surgery (Barker et al., 2010). Al-Hazmi showed *E. coli*, *Enterococcus* and *Pseudomonas* are the most common organisms isolated from blood infections (Al-Hazmi et al., 2014). In our study, the most prevalent bacteria isolated from mediastinitis was *S.aureus* as it was in the study of Ghotaslou et al which is similar to our findings (Ghotaslou et al., 2008).

In our study, among Gram-negative enterobacteriaceae, *E.coli* and *P. Aeruginosa*, and among Gram-positive bacteria *S. aureus* was the most common isolated bacteria. Lavakhamseh et al. showed that the most common bacterium isolated from patients with NIs was *E. coli* with 68.51% rate, and the highest resistance was found for Co-trimoxazole with 57.47% incidence (Lavakhamseh et al., 2014). In our study *E.coli* and *Enterobacter* .spp have shown high levels of resistance to Ceftazidime, Imipenem, Gentamicin and Amikacin respectively. Resistance to antibiotics among *P. aeuroginosa* was 16.6% to Ceftriaxone, Ceftazidime, Ciprofloxacin, Gentamicin, Amikacin, and Imipenem. Incidence of resistance to Ceftazidime, ceftriaxone and Ciprofloxacin among *Klebsiella*.spp was 71.42%, 57.1% and 57.1% respectively. Results in our study showed all *Acinetobacter*.spp were MDR. The rate of ESBL-producing bacteria was 14.28- 71.42% in our study. ESBL-producing bacteria confer significant resistance to penicillin, aztreonam antibiotics and narrow and extended-spectrum cephalosporin. They also frequently show resistance to aminoglycosides, trimethoprim/sulfamethoxazole and quinolones (Paterson et al., 2003). In consistent with our result, Rezai et al. reported 30.5% ESBL-producing *E.coli* (Rezai et al., 2015). Also the rates of extended-spectrum beta-lactamase production in *K. pneumoniae* and *E. coli* strains were determined as 14% and 6% respectively in Surucuoglu et al. study (Surucuoglu et al., 2005). ESBL-producing isolates have been responsible for provoking outbreaks in

many hospitals. Considering that these genes are located in plasmid they can spread in hospital environment.

S. aureus and *S. epidermidis* had high rates of antibiotic resistance. However resistance to vancomycin was observed in one isolated *S. aureus*. In our study, the rate of MRSA *S. aureus* was 54.2%. Azimian et al reported the incidence of MRSA *S. aureus* to be 47.5% (Azimian et al., 2012). Although Abdulgader showed that the proportion of Panton-Valentine leukocidin positive MRSA carriage infections ranged from 0.3 to 100% in humans (Abdulgader et al., 2015). MRSA is responsible for an increasing number of serious hospital and community-acquired infections. NIs with MRSA strains requires treatment with glycopeptide antibiotics which are nephrotoxic (Nelson et al., 2015; Pacheco et al., 2011).

Studies examining NIs bacteremia have shown that infection due to antibiotic-resistant pathogens is usually associated with greater patient mortality compared to the same infections attributed to antibiotic-sensitive bacteria (Chow et al., 1991; Rezai et al., 2012). It is necessary that infection control procedures be implemented carefully and antibiotic resistance patterns of organisms causing NIs should be checked periodically, specifically in heart surgery centers to guide empirical antibiotic therapies

5. Conclusions

Our study shows that although the rate of NIs following open heart surgery is within a reasonable limit, but MDR gram-negative bacteria and gram-positive bacteria are increasing. This issue can seriously affect the outcome of patients who underwent heart surgery. Therefore, using effective measures such as infection control, isolation of patients with MDR infections and implementation of antibiotic stewardship is recommended.

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Conflict of Interest

None declared.

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