

Utilization of Vibrating Mesh Nebulizer in the Treatment of Infants with Acute Bronchiolitis: A Randomized, Controlled Trial

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Abstract

Background: Bronchiolitis is a disease that is predominantly caused by the infection of peripheral airway due to respiratory syncytial virus (RSV). The occurrence is highly prevalent among childhood stage with seasonal outbreak peak during fall and spring. Treatment of bronchiolitis invariably involves lengthy hospitalization, which places significant socio-economic burden on family caregivers and healthcare system. Aerosolizing hypertonic saline using small-volume jet nebulizer (SVN) remains as one of the effective therapies to alleviate symptoms in infants with acute bronchiolitis. However, such approach not only restraints treatment to hospitalization and can irritate patients with loud noise. It is unclear whether an alternative aerosol therapy that offers similar efficacy yet enhances portability, convenience and quiet operation is available. **Materials and Methods:** Herein we showed that a vibrating mesh nebulizer (VMN) offered quiet delivery and undisturbed nebulization yet harnessed similar improvement in clinical symptoms in contrast with SVN when treating hospitalized infants with acute bronchiolitis. **Results:** A total of 64 hospitalized infants (<12 months of age) with acute bronchiolitis were enrolled. Subjects were randomly assigned to SVN (n=32) and VMN (n=32) groups and had received the same aerosol treatment protocol during hospitalization. Besides respiratory rate, the initial overall severity score; hospital stay duration; and intravascular-line day for both groups (SVN vs VMN) were similar. The data were 4.30±1.44 vs 4.92±1.3; 3.97±1.88 vs 3.94±1.66 days; 2.31±1.47 vs 2.16±1.46 days correspondingly. However, a higher satisfaction score (4.8/5) was shown in a corresponding questionnaire indicating user preference in VMN due to enhanced portability, ease of clean and operation, and less-noise. These advantages could potentially facilitate bronchiolitis treatment and follow-up maintenance at home. **Conclusion:** In sum, the treatment outcome for infants with acute bronchiolitis was equivalent between SVN and VMN. Easy portability and simple operation features of VMN may present a much favored therapeutic option for home care users.

Keywords: Bronchiolitis, infants, small-volume jet nebulizer, vibrating mesh nebulizer

INTRODUCTION

Bronchiolitis, a seasonal viral-induced lower airway infection, usually outbreaks in autumn and spring. The most common pathogen is respiratory syncytial virus, followed by human rhinovirus, parainfluenza virus, and human metapneumovirus, coronavirus, and adenovirus.^[1] It is highly prevalent among young children that typically result in substantial healthcare burden and hospital admission worldwide. Pathology of the disease comprises of diffuse inflammation and edema of bronchioles, mucus hypersecretion, necrosis, and sloughing of epithelial cells.^[2] The resulting clinical manifestation of bronchiolitis usually encompasses sputum over-production, crackles, wheezing, dyspnea, and even respiratory failure.

Except for some supportive care, there are only a few effective therapies for infants with acute bronchiolitis.^[3] Nebulizing hypertonic saline has been considered as a potential therapy. Several meta-analyses had supported that it could shorten hospital length of stay in hospitalized infants and improve the clinical severity score in both inpatients and outpatients.^[4,5] Concurrently, the American Academy of Pediatrics has recently recommended hypertonic saline nebulization treatment delivery to inpatient children with acute bronchiolitis.^[3]

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In traditional inhalation drug delivery, small-volume jet nebulizer (SVN) has been regarded as an inexpensive therapeutic approach to deliver aerosolized medications. Although SVN seems to be favored among young children who are in compliant with the usage of metered-dose inhaler, the resultant loud decibel generated; large residual volume postadministration, and inconsistent drug concentration throughout delivery significantly impedes the widespread acceptance among young children population. Hence, a more affable nebulization methodology is in great need. With the advent of vibrating mesh nebulizer (VMN), it has shown surpassing advantages over conventional SVN, including (1) stable and high aerosol output efficiency; (2) delivery of high-quality fine-particle aerosol; (3) low-residual nebulizer-solution volume; (4) ability to deliver ultra-small volume; and (5) provide undisturbed and quiet administration.^[6,7] Given clear benefits, the possibility of delivering medication through VMN to patients with bronchiolitis remained uncertain.

Although VMN can successfully deliver bronchodilators, inhaled corticosteroids, and antibiotics,^[8] the administration of hypertonic saline aerosols to infants with acute bronchiolitis has not heretofore been demonstrated. In the study, we investigated the therapeutic effects of VMN and SVN in nebulizing hypertonic saline to treat infants with acute bronchiolitis. The primary outcome examined the length of hospital stay. User experience analysis of VMN was the secondary outcome.

MATERIALS AND METHODS

Patients

The current study was performed at Chang Gung Memorial Hospital from March 2015 to March 2016. Children that were 12 months or younger; diagnosed with acute bronchiolitis and hospitalized were eligible for the study. The diagnosis of bronchiolitis was defined as a history of viral upper respiratory tract infection plus wheezing and/or crackles on chest auscultation with respiratory distress. This study was approved by the Chang Gung Ethics Committee [Figure 1]. The written informed consents were obtained from parents or legal guardians of the infants. Records and clinical information of all patients were anonymized and deidentified before analysis. Children born prematurely (gestational age <36 weeks), those with major birth defects or congenital structural anomalies of the upper airway or neuromuscular disorders, those who were hemodynamically unstable, and those with a history of severe lower airway infection with intensive care unit admission were excluded from the study.

Study design

After enrollment, all infants admitted to the hospital were treated according to the same clinical pathway, i.e., nebulized hypertonic saline, to ensure consistent care and minimize data variation. Nebulizers (SVN or VMN) were randomly assigned by simple randomization table as the device for delivering hypertonic-saline aerosol. The flow chat of enrollment was

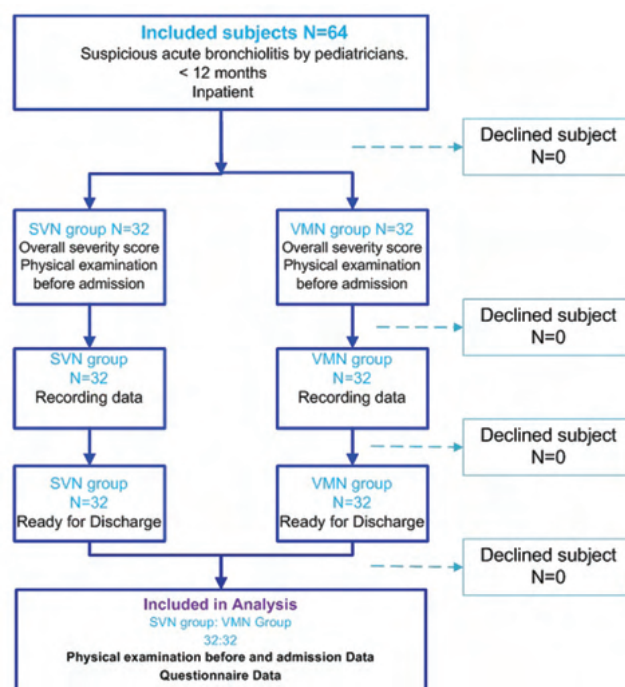


Figure 1: Flow chart of enrollment.

shown in Figure 1. SVN and VMN used in this study were from Gale Med Nebulizer Kits (GaleMed Corporation, Taipei, Taiwan) and PocketAir™ Portable Nebulizer (MicroBase Technology, Taoyuan, Taiwan), respectively. The delivery of hypertonic-saline aerosol prescription was designed as 4 ml of 3% saline solution (three times a day) using nebulizer.

After admission, respiratory rate, heart rates, respiratory effort, and oxygen saturation (while breathing room air) were observed and recorded daily till discharge. Daily infant conditions such as respiratory rate, oxygen saturation, and respiratory effort (classified as mild, moderate, or severe in accord to daily severity score) were presented in Table 1. The total hospitalized duration and supplemental intravenous fluid were also documented after discharge. In addition, a questionnaire regarding the usage of VMN device was completed for VMN enrollment group. A total of five items pertaining quality of device (i.e., weight, aerosol flow, noise in operation, ease of cleaning, and performance) were main assessments within questionnaire. The total score ranged from 0 to 5 and the full mark was 5.

Particle characterization

Particle characteristics generated by SVN and VMN were measured with Spraytec (Malvern Instruments, UK). In brief, 4 ml of 3% hypertonic saline solution was added to medication cup of SVN or VMN. SVN was driven by compressed air from a gas cylinder at 8 L/min. On nebulization, particle characteristics were measured by Spraytec for 75 s. After that, several parameters, including volume diameters (Dv10, Dv50, and Dv90), relative span factor (RSF), and percentage of droplet volume under 5 μm was used to compare

the difference between SVN and VMN. Dv10, Dv50, and Dv90 represented 10%, 50%, or 90%, respectively, of droplet volume in diameter smaller or equal to the stated value. RSF was calculated by $(Dv90-Dv10)/Dv50$ and which represented the uniformity of the droplet volume distribution. The results of triplicate run for four samples of either SVN or VMN were collected and compared. $P < 0.05$ was considered to be statistically significant.

Statistical analysis

Results were expressed as mean \pm standard error values. Statistical comparisons between groups were performed

Table 1: Overall Severity Score and normal range of respiratory rate depending on different age

Overall severity score	a + b + c		
	<2 Mild	2-3 Moderate	>3 Severe
a. Respiratory-effort scores			
Score			
0		Not present	
1		Mild-to-moderate	
2		Severe	
Weighted scores			
1		Intercostal recession	
1		Subcostal recession	
1		Substernal recession	
1.5		Tracheal tug	
1.5		Nasal flaring	
Respiratory-effort scores			
0		0-4.9 Mild	
1		5.0-8.9 Moderate	
2		9.0-12.0 Severe	
b. Oxygen saturation breathing ambient air			
0		95%-100% Moderate	
0		90%-94% Moderate	
1		<90% Severe	
c. Respiratory rate compared with that age of healthy			
0		<2 SD	
1		2-3 SD	
2		>3 SD	
Normal range of respiratory rate			
Age (months)	Mean \pm SD		
	Awake	Sleep	
0-2	48 \pm 9.1	39.8 \pm 8.7	
2-6	44.1 \pm 9.9	33.4 \pm 7.0	
6-12	39.1 \pm 8.5	29.6 \pm 7.0	

SD: Standard deviation

using Mann–Whitney test for continuous variables, and Fisher exact test for categorical variables. $P < 0.05$ was considered statistically significant. Comparisons of hospitalization days, intravenous fluid administration days, and oxygen supplement between groups were performed by Student’s *t*-test. All analyses were performed using IBM SPSS software v. 20 (Armonk, NY, USA).

RESULTS

A total of 64 infants (32 patients in each of SVN or VMN group) were enrolled in this study [Figure 1]. The demographic and baseline clinical severity of both groups were shown in Table 2. Despite an overall male predominance in both groups (SVN group 62.5%; VMN group 65.6%), the demographic data were similar across SVN and VMN groups [Table 2]. Except for the higher score of respiratory rate in VMN group, the remaining baseline clinical characteristics were statistically equivalent between patients that were enrolled into SVN or VMN group [Table 2].

We first tested whether VMN could engender an overlapping clinical outcome concerning severity score, oxygen saturation, and respiratory rate throughout hospitalization when compared with SVN. Figure 2 showed that the values across three different parameters were consistently maintained from day 1 till discharge and that no significant inter-device deviation was observed.

We then investigated whether VMN was able to establish matching primary clinical outcome when compared with SVN. Patients treated with the same clinical pathway yielded comparable length of hospital stay irrespective of device groups (SVN vs. VMN, 3.97 ± 1.88 vs. 3.94 ± 1.66 days; [Table 3]). Moreover, other confounding factors potentially interfering with the length of hospital stay were also considered. For instance, paramedical complications, such as but not limited to, administrative and social/behavioral factors, have been shown to disturb hospitalized duration thus, we explored the days of intravenous-fluid supplement. Table 3 showed that SVN versus VMN was 2.31 ± 1.47 versus 2.16 ± 1.46 days correspondingly and that no difference was found.

While, different devices had generated parallel clinical outcomes, our study further examined if VMN had preferential improvements on various physiological parameters. According to Table 4, patients treated with VMN revealed more significant improvements in overall severity score, respiratory effort, and respiratory rate, in respect to SVN. Other physiological remained unchanged.

After treatment period, questionnaires exploring user experience feedbacks were included in the current study. A total of 62 questionnaires (SVN, $n = 32$; VMN, $n = 30$) were received from guardians of enrollers in both groups. The mean scores of SVN and VMN group were 3.3 and 4.8 (out of 5), respectively. Our data showed that guardians were particularly

satisfied with the portability, ease of cleaning and usage, and the quiet operation features provided by VMN. There were, however, 5 guardians who had suggested that the aerosol flow rate generated from VMN could be minimized for infant application. Nonetheless, difficulty in clearance ($n = 18$), noisy

operation ($n = 13$), strong aerosol flow ($n = 10$), and poor performance ($n = 10$) were among the common complaints for SVN.

Finally, to understand critical differences in functional performance between two devices, we compared aerosol generation capacity. Figure 3 indicated that aerosol diameter in ranges of Dv50 ($P = 0.35$) and Dv90 ($P = 0.14$) delivered by both devices was relatively similar. The percentage of hypertonic saline aerosol $<5 \mu\text{m}$ generated by SVN and VMN were 52.56 ± 5.4 and 48.7 ± 1.91 ($P = 0.25$), respectively. No significantly difference was found. However, it was evident that the span of aerosol diameters (RSF) was narrower for VMN (1.46 ± 0.1) than SVN (2.07 ± 0.12). Therefore, VMN data had demonstrated a tighter and more concentrated (higher volume frequency) aerosol range that was characteristic of better aerosol quality [Figure 3].

Table 2: Baseline clinical characteristics

	SVN group	VMN group	P
Age (month)	5.69±3.03	6.66±2.85	0.944
Male:female	20:12	21:11	0.798
BH (cm)	67.39±10.7	68.11±6.93	0.460
BW (kg)	9.42±9.64	8.13±1.67	0.751
Baseline overall severity score	4.30±1.44	4.92±1.31	0.652
Respiratory-effort scores	4.27±1.46	4.83±1.37	0.866
SpO ₂ scores	0.03±0.18	0.06±0.25	0.243
Respiratory rate (score)	0	0.03±0.18	0.043

SVN: Small-volume jet nebulizer, VMN: Vibrating mesh nebulizer, BH: Body height, BW: Body weight

Table 3: Primary outcome

	SVN group	VMN group	P
Hospital stay day	3.97±1.88	3.94±1.66	0.944
Overall severity score (at discharge)	2.55±1.16	2.59±1.07	0.654
IV days	2.31±1.47	2.16±1.46	0.671

SVN: Small-volume jet nebulizer, VMN: Vibrating mesh nebulizer, IV: Intravenous

DISCUSSION

Recent studies have demonstrated the usage of SVN in delivering aerosolized saline to treat patients with acute bronchiolitis. However, due to limitations associated with traditional SVN, the possibility of administering aerosol through VMN to achieve equivalent therapeutic goal has yet to be established. Herein, we showed for the first time that VMN could successfully nebulize hypertonic saline medication in treating hospitalized young children (infants) with acute bronchiolitis.

Table 4: Recording physiological parameters during hospitalization

	SVN group			VMN group		
	Admission	Discharge	Difference [#]	Admission	Discharge	Difference [#]
Overall severity score	4.30±1.44	2.55±1.16	-1.75±1.55	4.92±1.31	2.59±1.07	-2.33±1.35*
Respiratory-effort scores	4.27±1.46	2.52±1.13	-1.72±1.54	4.83±1.37	2.56±1.08	-2.27±1.29*
SpO ₂ scores	0.03±0.18	0.03±0.18	0.0±0.04	0.06±0.25	0.03±0.18	-0.03±0.31
Respiratory rate (score)	0	0	0	0.03±0.18	0	-0.03±0.18*
SpO ₂ value (%)	98.13±1.86	97.41±1.9	-0.72±2.12	97.34±2.04	97.41±3.68	+0.44±2.14
Heart rate (min)	143.8±21.1	131.9±18.5	-12.0±19.0	140.7±14.7	130.2±15.9	-10.5±17.6

* $P < 0.05$, [#]Comparing VMN group with SVN group. SVN: Small-volume jet nebulizer, VMN: Vibrating mesh nebulizer

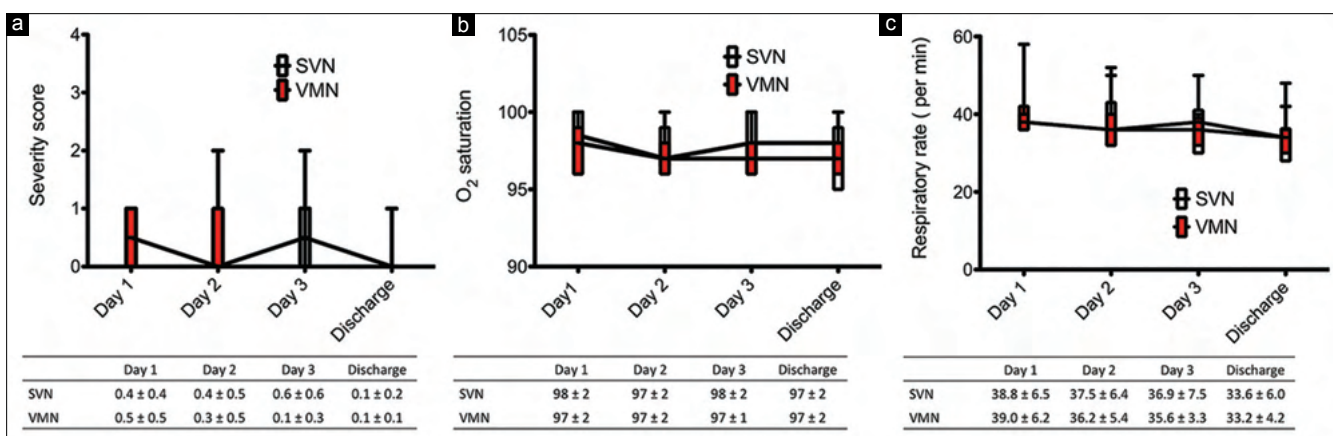


Figure 2: Clinical trend, (a) Respiratory-effort scores (b) oxygen saturation (c) respiratory rate, after admission.

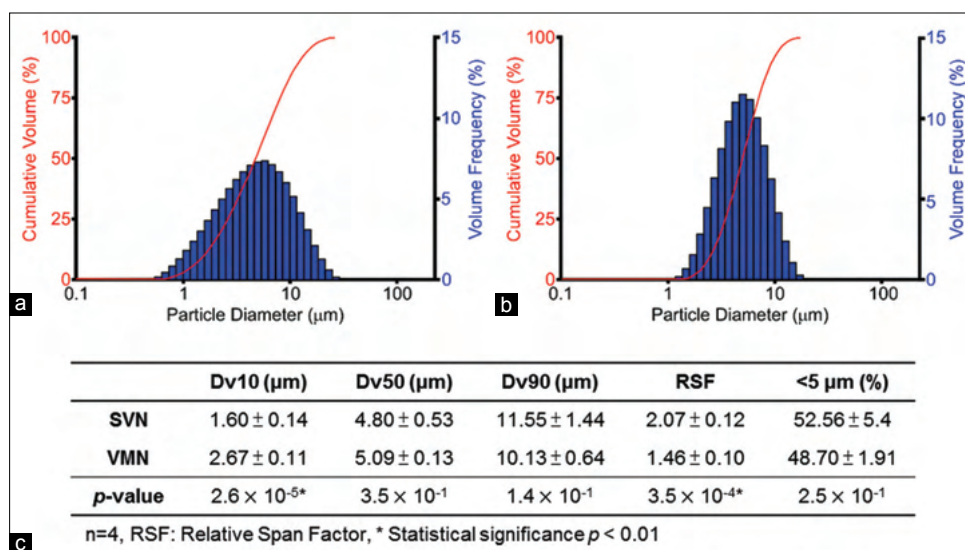


Figure 3: Particle characteristics of SVN and VMN. (a) Drop size distribution of SVN. (b) Drop size distribution of VMN. (c) Particle characteristics comparison of SVN and VMN. SVN: Small-volume jet nebulizer, VMN: Vibrating mesh nebulizer.

Aerosol generated from hypertonic saline is known to minimize airway edema, reduce mucus plugging, improve mucociliary clearance, and rehydrate epithelial surface in infants with acute bronchiolitis.^[9] A large meta-analysis has confirmed that patients inhaling hypertonic saline aerosol showed significantly reduced hospitalization period (-0.45 days) than those receiving isotonic saline nebulization.^[4] As of now, the predominant choice of delivery has been confined to jet nebulizers (SVN) for cost-effective reasons. Nonetheless, such device inevitably suffers from slow delivery rate; external compressor requirement during operation; noisy nebulization; uneven drug concentration; drug temperature variation; significant residual volume; and inability to be reprocessed. Consequently, the aforementioned shortcomings severely hinder SVN application in young children population. To circumvent the dilemma, vibrating mesh technology has been shown to achieve parallel, if not even better, therapeutic efficacy; thus, making the substitution with VMN highly likely. Our trial therefore had evaluated the differences in clinical outcome presented by infants with acute bronchiolitis after inhaling hypertonic saline delivered by either SVN or VMN.

We first tested if different nebulization methodologies (SVN and VMN) would affect hospital stay duration. Table 3 showed no significant differences in length of hospital stay. Our average hospital stay data (3.96 ± 1.78 days) was supported by a meta-analysis report documenting that the length of hospital stay was approximately 2.2–5.8 days for hypertonic saline group. Moreover, results from Table 3 further illustrated that device-dependent effect on overall severity score and intravenous infusion period was insignificant due to overlapping data range. Interestingly, despite the nondifferential effects on clinical outcome between both treatment groups, VMN treatment seemed to have produced more significant improvements in overall

severity score, respiratory effort, and respiratory score [Table 4]. The outcomes suggested that both devices have equivalent performance as shown by analogous clinical outcome. We surmised that the high degree of resemblance in clinical outcome could be attributed to an intersecting range of aerodynamic diameters of saline aerosol. Data from Figure 3c has verified that size range of hypertonic saline aerosol (Dv50, Dv90 and <5 μm [%]) generated by both devices had coincided. In support of our analysis, reports have also documented that other commercially available VMN could deliver similar inhaled mass and median aerodynamic diameter as jet nebulizer.^[10] Figure 3a and b also reported that VMN displayed a narrower aerosol size range (RSF) with better quality and more concentrated output which could potentially explain the enhanced improvement in clinical severity among patients with bronchiolitis [Table 4]. Finally, the elevated satisfactory score for VMN group signified that device friendliness and convenience were the critical parameters contributing to user preference.

Our clinical trial outcome was corroborated by prior studies detailing the advantages of VMN such as, but not limited to, small size, portability, convenience, and silent operation. These properties were strongly advocated when applied to treatment for children population.^[10,11] While VMN has been authenticated to deliver a wide range of medications including bronchodilators, corticosteroids, or antibiotics aerosols for elder children with asthma or cystic fibrosis;^[8,12,13] nonetheless, our study was the first to demonstrate successful VMN employment to young children population by offering comparable, if not even better, therapeutic improvements on clinical severity, when compared with SVN. Together with apparent operational advantages that were preferentially favored among parents/guardians of patients, VMN could be well suited for aerosol therapy in young children suffering from acute bronchiolitis.

There were some potential limitations in our current study. First, the patient number could be enumerated to enhance the validity of clinical findings. Although the sample size ($n = 32$) of each group was relatively small, the statistical power was able to achieve 0.7 in the *post hoc* analysis. To definitely clarify therapeutic efficiency, our clinical trial could be strengthened by quantifying *in vivo* deposition of delivered aerosol in patients using scintillator. The proposition was supported by previous experiments claiming that VMN could achieve higher lung deposition.^[11] Moreover, since VMN group had displayed a higher baseline of a respiratory severity score, the analysis of clinical severity improvement could be biased. Such problem could be eliminated by expanding enrollment and perform further investigation. Finally, apparent user preference shown by questionnaire might be biased due to the esthetically designed novel VMN, possibly tempering with objectivity. However, significant residue, uneven delivery, and noise were the major drawbacks of SVN.

CONCLUSION

Our study exhibited that VMN offered equivalent treatment efficacy and clinical effects in acute young children with bronchiolitis receiving hypertonic saline nebulization when contrasting with SVN. Majority of parents/guardians praised the operational experience provided by VMN. Therefore, VMN may serve as an alternative yet advanced option when delivering aerosolized medication, targeting a wider population spectrum, for various respiratory disorders in different environments.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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