Markers of Myocardial Dysfunction in Neonates with Sepsis of Various Gestational Age

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Abstract

Introduction: Nowadays, the issues of early diagnostics of cardiovascular disorders in neonates with sepsis with the use of up-to-date methods of examination that can be applied as screening methods with the aim to verify the possible development of cardiovascular dysfunction remain urgent. To study certain clinical-instrumental parameters and biochemical markers in neonates depending on the gestational age to improve the prognosis with neonatal sepsis (NS). **Materials and Methods:** To realize the objective, 57 neonates were under our observation with verified diagnosis "NS." I Group (23 patients – 40.3%) included neonates with the term of gestation 37–42 weeks, II Group– 34 preterm neonates (59.7%) with gestational age under 36 weeks inclusive. The latter group was subdivided depending on the term of gestation into IIA subgroup including 21 preterm neonates with NS and the term of gestation 32–36 weeks, IIB-subgroup included 13 neonates born in the term under 32 weeks of gestation. **Results:** Term males were found to suffer from sepsis more often (odds ratio = 5.19). Delivery by cesarean section for preterm neonates increased reliably the risk of NS development compared with term neonates (OR = 2.7). It was found that the average values of LDH activity in the groups were not higher than normal parameters with a tendency to decrease as the duration of pregnancy decreased. At the same time, in almost all examined patients, there was an excess of serum activity of Creatine phosphokinase-MB fraction (CPK-MB) (86.96% of cases in Group I and in 91.18% of cases in Group II) and in some patients an increase in serum aspartate aminotransferase (ACT) activity in 52.17% of patients with Group I, in 47.06% of cases from Group II, $P > 0.05$). The correlation analysis conducted showed that in preterm neonates suffering from NS increase of the myocardial functional ability of the left ventricle was associated with females and the number of days of inotropic support. **Conclusions:** Analysis of clinical-anamnestic findings determined that term males suffer from NS reliably more frequent which is clearly associated with the risk of NS development. Increase of CPK-MB serum activity can be considered as a sign of myocardial dysfunction development caused by NS. The analysis of echocardiographic parameters conducted in the group or preterm neonates found a direct correlation of the ejection fraction with initiation of cardiovascular resuscitation immediately after birth and the period of introduction of inotropic drugs.

Keywords: Cardiovascular system, neonatal sepsis, neonate

Introduction

Neonatal sepsis (NS) remains one of the major causes of sickness and mortality in the neonatal age.[1] According to the world literature data, it is estimated as 1–10 cases per 1000 of live-births, and among patients in the intensive care units occurrence of sepsis is 25%–30% with lethal outcome of 13%–50%. NS remains the major cause of losses among patients in severe conditions at the departments of neonatal resuscitation units. Epidemiological studies of sepsis occurrence and mortality rate due to it vary in the world considerably,[2] including the countries with different income levels. At the same time, worse prognosis of NS in the cohort of preterm neonates and those born with intrauterine retardation are a well-known fact.[3] These neonates are characterized by physiological and in particular immunological immaturity; they require a long hospital stay and doing invasive procedures concerning their care and treatment.[4] Sepsis occurrence is the highest among infants born with extremely low body weight.[5]

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Cardiac dysfunction in neonates associated with sepsis is not studied as well as that of the adult patients, whose myocardial dysfunction is rather spread with the frequency of registration ranging from 10% to 70%.[6] The researchers explain it due to the lack of clinical consensual definition of cardiovascular dysfunction associated with sepsis, although it deteriorates considerably the outcome of treatment.[7,8] The literature available contains rather limited number of studies dealing with sepsis-induced myocardial dysfunction in neonatology.[9] They mainly consider sepsis in pediatric practice,[10,11] while cardiac dysfunction occurs more often among neonates and infants with sepsis compared with adult patients.[12]

Myocardial dysfunction mediated by sepsis is one of the most common components of multiple organ inequality in case of severe sepsis and septic shock,[13] occurrence of left ventricular systolic dysfunction (LVSD) with severe pediatric sepsis ranges within 20%–60%.[14] Diagnostic echocardiographic criteria of LVSD are left ventricular ejection fraction (EF), which with values <50% can associate with unfavorable consequences of severe sepsis.[15] Maximal severity of myocardial dysfunction occurs primarily on the 1–3 day of the disease, and restoration from 7 to 20 days of the disease.[10] Myocardial dysfunction caused by sepsis, so-called "septic cardiomyopathy,"[16] is less reported in neonatology, and in case of NS with different term of gestation in particular. To study certain clinical-instrumental parameters and biochemical markers in neonates depending on the gestational age to improve the prognosis with NS.

Materials and Methods

To realize the objective, 57 neonates were under our observation with verified diagnosis "NS" on the base of the neonatal resuscitation unit, department of neonatal pathology and care department for preterm infants at Chernivtsi Regional Children Clinical Hospital.

The general characteristic of the groups is presented in Figure 1 and Table 1.

The differences found between the groups by their gestational age and parameters of physical development were considered natural. They reflect correct formation of the groups and subgroups of comparison. Table 1 shows that an average age of mothers in the groups and subgroups of comparison did not differ substantially (in all the cases $P > 0.05$). Statistically considerable differences between an average age of parents of patients with NS among children of clinical groups and subgroups of comparison were not found. Among term neonates, males suffered from sepsis reliably more often, and such regularity was not found among preterm neonates. Delivery by cesarean section was found more often in the group of preterm neonates.

Examination and treatment of patients with NS was performed according to the modern international instructions and recommendations.[17-19]

In addition to clinical examination on the basis of biochemical laboratory of Chernivtsi Regional Children Clinical Hospital using the biochemical analyzer HTI BioChem FC-200 (USA) and reagents produced by the firm «Cormay» (Poland) all the neonates underwent biochemical detection of markers of ischemic myocardial lesion in the blood serum focused on the literature standard of the markers examined.[20] Thus, lactate dehydrogenase activity (LDG, norm to 576 UN/L) was determined considering recommendations of the German Association of Clinical Chemistry, creatine phosphokinase-MB fraction (CPK-MB, norm 24 UN/L) and aspartate aminotransferase (AST, norm to 40 UN/L) were examined according to the recommendations of the International Federation of Clinical Chemistry.

To study the myocardial functional state, electrocardiography (ECG) was used in the standard Einthoven's leads (I, II, and III), in the intensified Goldenberg unipolar leads from the extremities (aVR, aVL, aVF) and in 6 precardial Wilson's leads (V1-V6) with the rate of tape 50 mm/s. ECG was made

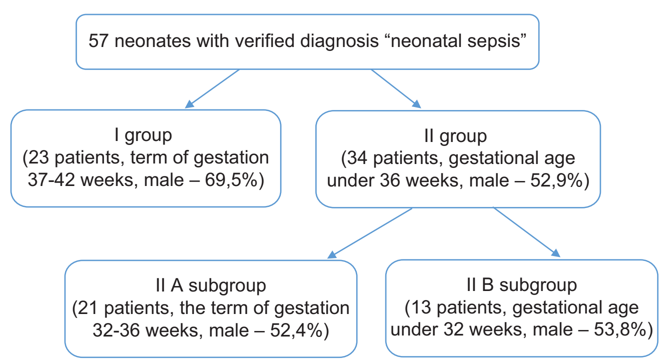

Figure 1: Distribution of patients into clinical groups based on the the term of gestation

Table 1: General characteristic of groups and subgroups of comparison (M±m)

Parameter	I group (n=23)	II group (n=34)	II A subgroup (n=21)	II B subgroup (n=13)
Term of gestation, (weeks)	38.6±0.28	32.3±0.43	34.1±0.21	29.6±0.43
Body weight at birth, (g)	3279.3±109.34	1809.5±85.66	2103.3±81.91	1335.1±65.81
Body length at birth, (cm)	52.5±0.76	42.1±0.75	44.3±0.65	38.5±1.07
Cesarean section, n (%)	6 (26.1)	19 (55.9)#	11 (52.4)#,+	8 (61.5)#
Mother's age, (years)	30.1±1.61	29.5±1.12	30.1±1.42	28.7±1.86

#Concerning I group *P<0.05 I:II, ** P<0.05 IIA:IIB on the electrocardiograph Nihon Kohden Cardiofax C (Japan) after feeding of a neonate. Electrocardiograms were registered and assessed according to the methods generally recognized in neonatology, duration of PQ interval and the major waves (P, R, and S) were determined. All the parameters were compared with the parameters of healthy neonates of the appropriate term of gestation.

Echocardiographic examination (Echo-CG) of neonates was made on the ultrasound device «PHILIPS HD11 XE» with ultrasound sensor frequency 2.5–5 MHz, according to the standard methods in the one-and two-dimensional regimens evaluating the following morphometric parameters: End-diastolic volume, left atrial diameter in diastole, and left ventricular posterior wall thickness (LVPWT) in diastole. Left ventricular systolic function was assessed on the basis of the volumes of EF and shortening fraction (SF).

The study was carried out by means of case–control method in the parallel groups using simple random sampling with a written consent of parents. The results of the study obtained were statistically processed by means of the methods of variation statistics calculating arithmetic mean (M) and standard error of the mean (m). Correlation between qualitative parameters was measured by the Pearson test calculating connection relation ® and its probability (P). The parameters of clinical-epidemiological risk were assessed by calculation of odds ratio (OR) of the event and relative risk (RR) considering their 95% confidence interval (95% CI) and the value of attributive risk (AR). The actual data were processed statistically by means of the software StatSoft Statistica v 6.0. with the known number of observation (n). Critical significance level «P» in checking statistical hypotheses in the study was considered with $P < 0.05$.

Ethical committee approval code and details

The research protocol and informed consent form were approved by the Commission on Biomedical ethics in Biomedical Scientific Research of the Bukovinian State Medical University (Protocol No. 7 dated April 19, 2018, Protocol No. 5 dated February 18, 2021).

Informed consent

Written and oral informed consent was obtained from all individual participants included in the study.

Results

As it is mentioned above, term males suffered from sepsis more often. Males were associated with the following risk parameters of NS development: OR– 5.19 (95% CI 2.84–9.48), RR – 2.28 (95% CI 1.64–3.15), AR–0.39). Delivery by cesarean section for preterm neonates increased reliably the risk of NS development compared with term neonates: OR–2.7 (95% CI 1.48–5.0), RR–1.54 (95% CI 1.07–2.22), AR–0.24.

According to the medical documents of the maternity homes and obstetrical departments severity of disorders of general condition of the examined neonates was assessed as severe in 47.8% of neonates from I Group, in 88.2% cases in Group II ($P_{I:\ II} < 0.05$), in 85.7% representatives from IIA subgroup ($P_{I:\ IIA} < 0.05$) and in 92,3% of infants from IIB subgroup ($P_{I:\ IIB} < 0.001$). Severity of the condition was stipulated by available signs of respiratory failure of II-III degrees and instable hemodynamics. On the basis of the data presented, the most marked severity of general state disorders at birth was peculiar for neonates with the shortest term of gestation. Thus, concerning neonates from Group I preterm birth increased chances of severe general condition of patients with NS: OR–8.16 (95% CI 3.96–16.82), RR–3.52 (95% CI 2.83–4.37), AR = 0.46. These parameters of the clinical-epidemiological risk of severe condition at birth for the term of gestation 32–36 weeks were the following: OR-6.54 (95% CI 3.30–12.97), RR–2.88 (95% CI 2.39–3.72), AR–0.43, and for the patients from IIB subgroup relatively I group they were respectively: OR–13.09 (95% CI 5.69–30.12), RR–5.12 (95% CI 4.14–6.34), AR–0.53.

Every third infant was found to require the measures of cardiopulmonary resuscitation in the delivery room (30.4%) of Group I, 67.6% neonates from Group II (P_{I}: $_{II} < 0.05$), half (52.4%) of the representatives from IIA subgroup (P_{II}: $_{IIA} < 0.01$) and all the seriously sick (92.3%) from IIB subgroup (P_{I}: $_{IIB}$, $_{IIA}$: $_{IIB} < 0.05$). Therefore, concerning term neonates the risk of this valuable postnatal factor NS increased reliably: For II Group: OR–4.77 (95% CI 2.63–8.68), RR–2.17 (95% CI 1.57–3.0), AR = 0.37; and for preterm neonates with the term of gestation <32 weeks (IIB subgroup) respectively: OR–27.44 (95% CI 11.73–64.19), RR–7.55 (95% CI 5.58–10.21), AR-0.65. It should be noted that in the group of preterm neonates with NS the need to conduct resuscitation in the delivery room increased with shorter term of gestation of neonates and was for the representatives from IIB subgroup the following: Concerning II Group: OR–5.75 (95% CI 2.46–13.39), RR–3.0 (95% CI 2.60–3.48), AR = 0.39; and concerning IIA Subgroup: OR–10.89 (95% CI 4.73–25.06), RR–4.58 (95% CI 3.77–5.57), AR = 0.50.

To stabilize general condition, a part of the representatives from groups and subgroups of comparison immediately after birth required volume load occurring in 26.1% cases in Group I, in 61.7% cases in Group II (P_{I}: $_{II} < 0.05$), in 57.1% children from IIA subgroup (P_{I}: $_{IIA} < 0.05$) and 69.2% neonates from IIB subgroup (P_{I}: $_{IIB} < 0.05$). Therefore, as far as gestational age decreased the need to carry out volume load at birth increased. Thus, concerning the term neonates the risk of the event increased for the infants from II group: OR–4.56 (95% CI 2.50–8.32), RR–2.06 (95% CI 1.43–2.96), AR = 0.36; for the patients from IIA subgroup: OR–3.77 (95% CI 2.08–6.84), RR–1.87 (95% CI 1.29–2.71), AR = 0.32; and for the neonates from IIB subgroup: OR–6.36 (95% CI 3.44–11.78), RR–2.47 (95% CI 1.73–3.52), AR-0.43.

One of the important prognostic criteria is child's condition immediately after birth according to Apgar score. Table 2

Table 2: Results of assessment by apgar score of the patients' condition from clinical groups of comparison (M±m)

Clinical groups and subgroups	Number of children	Average score at the 1st (min)	Average score at the 5th (min)
I group	23	6.47±0.30	7.26±0.47
II group	34	5.94±0.21	6.17±0.37
IIA subgroup	21	6.14±0.27	6.85±0.20
IIB subgroup	13	5.61±0.31	5.07±0.85
Pt		I:IIB, IIA:IIB <0.05	I:II, I:IIB <0.05

Pt: Student criterion

presents comparative parameters of neonatal adaptation according to Apgar score at the 1st and 5th min of life.

Therefore, term neonates better adapted to the conditions of the postnatal life, and these processes were worse for preterm infants. Moreover, the term of gestation <32 weeks was associated with their negative tendency. Appropriately, these patients required longer inotropic support of cardiac activity under conditions of maternity-obstetrical institution. Thus, under conditions of intensive care units of the maternity home 21.7% representatives from I Group received daily average dose of dobutamine (6.25 ± 1.25) mcg/kg/minute during (1.8 ± 0.48) days of treatment, in 26.5% of children from II Group these parameters were (4.67 ± 0.75) mcg/kg/min during (4.44 ± 0.58) days ($P_{I:II}$<0.05). Depending on the term of gestation, the parameters of inotropic support were: In 23,8% neonates from IIA subgroup– (5.2 ± 1.28) mcg/kg/min during (3.6 ± 0.87) days ($P_{I:IIA}$=0.05), and in 30.8% patients from IIB subgroup– (4.0 ± 0.57) mcg/kg/min during (5.5 ± 0.28) days ($P_{I,\ II,IIA:IIB}$<0.05).

Table 3 presents the results of biochemical examination of the blood serum in neonates from the clinical groups and groups of comparison.

Discussion

The intracellular cytoplasmic enzyme lactate dehydrogenase (LDG) is known to catalyze inter-conversion of pyruvate and lactate – the process essential for the production of adenosine triphosphate (ATP).[21] An increased serum content of LDG is associated with tissue breakdown, since in the majority of tissues (especially in the muscular one) activity of this enzyme is 500–700 times higher than in the blood serum.[22] The results obtained showed that average values of the enzyme activity in the groups were not higher than the normal parameters with the tendency to decrease as far as the term of gestation decreased. Thus, LDG activity >576.0 UN/L was found in 43.48% term neonates and 32.35% of preterm infants, including 42.86% of neonates with the term of gestation more than 32 weeks and only in 15.38% of representatives from IIB subgroup ($P_{I:\ IIB}$ < 0.05).

Distribution of CPK-MB values was indicative of the fact that practically all the examined patients (86.96% cases in I Group, in 91.18% cases in II Group) presented excess of serum activity of the enzyme. Creatine phosphokinase is a complicated system of enzymatic isoforms.[23] Its activity is proportional to myocardial load and closes associates with cardiac activity, since it is responsible for the transmission of the major part of energy flow from mitochondria to ATPes under normal physiological conditions in the cells.[24] Therefore, the results obtained can be considered an indirect evidence of development of energy-dependent myocardial dysfunction caused by NS.

Increased serum activity of AST occurring in 52.17% patients from I Group, in 47.06% cases from II Group (in 52.38% cases of IIA and in 38.46% cases of IIB subgroups in particular) (in all the cases $P > 0.05$) was explained from the positions of effect produced by hypoxia during delivery, which causes release of a number of mediators from the vascular endothelium (fibronectin, thrombomodulin, endothelin-1, and thromboxane), resulting in narrowing of the vessels and secondary multiple organ hypoxia.[25]

A supposition can be suggested that intensification of synthesis processes and energy transition in the myocardial cells in all the patients with sepsis demonstrated less active inflammatory cascade followed by destruction of cells and release of enzymes (LDG and AST) in preterm neonates with NS. Thus, disorders of the immune response in the loci of infection elimination and higher level of bacteremia in neonates suffering from sepsis can result from a so-called "tolerance to microbes."[26] It enables to reduce energy intake which agrees with less energy supplies in preterm neonates, promotes avoiding transition into the catabolic state which deteriorates growth, and is favorable for establishment of symbiotic microbiota.

The group of preterm neonates presents statistically reliable correlation of the gestational age with LDG activity in the blood serum ($r = 0.37$, $P = 0.014$), the signs of left ventricular overload on ECG ($r = 0.41$, $P = 0.036$), and volume load with primary stabilization of the condition and LDG activity ($r = -0.38$, $P = 0.03$). LDG activity in term neonates possessed feedback with initiation of inotropic support ($r = -0.49$, $P = 0.023$), and AST–with Apgar score at the 5th min of life ($r = -0.54$, $P = 0.021$). Contrary to the latter, AST activity in the blood serum of preterm neonates possessed direct correlations with Apgar score at the 1st min of life ($r = 0.46$, $P = 0.048$) and the 5th min of life ($r = 0.48$, $P = 0.04$).

Echocardiography was performed for all the patients with NS before they were transported to the neonatal resuscitation unit after their condition was stabilized in the maternity homes. On the basis of it, the results of the study can be interpreted as myocardial response to the therapeutic measures conducted.

Table 4 presents the results of the major parameters of echocardiography in children of the clinical groups of comparison.

According to modern results of scientific studies, patients with refractory septic shock may have low, normal or high cardiac output (by echocardiography findings), since hemodynamic parameters of the cardiac output and systemic vascular resistance are not uniform and develop with time in response to inotropic and vasopressor support.[27,28] Wide ranges of myocardial dysfunction frequency can be caused by the difference in patient selection, successful resuscitation in anamnesis, time between the onset of the disease and examination conducted, the use of other echocardiographic parameters with various boundary values, inotropic characteristic and myocardial sensitivity to it, pulmonary ventilation (cardiac-pulmonary interaction) etc.[29] Detected growth of the heart morphometric characteristics as far as gestational age of patients increases agreed with modern literature data, and higher parameters of EF in preterm neonates concerning infants from I Group were considered as a sign of activation of the adaptation-adjacent mechanisms.[30] The correlation analysis conducted showed that in preterm neonates suffering from NS increase of the myocardial functional ability of the left ventricle was associated with females (for EF r = 0.94, P = 0.0001, for SF– r = 0.94, P = 0.0001) and the number of days of inotropic support (for EF r = 0.68, P = 0.043, for SF– r = 0.71, P = 0.03). At the same time, LV posterior wall thickness correlated with the body length (r = 0.72, P = 0.03), and the results of SF among the neonates from IIA subgroup were associated with the head circumference (r = −0.88, P = 0.05). It is interesting to note that correlations of EF and SF with females were found in IIA subgroup only (for EF r = 0.96, P = 0.01, for SF– r = 0.91, P = 0.03), but they were lacking with the term of gestation <32 weeks. These preterm neonates presented reverse correlations of SF with the body weight (r = −0.99, P = 0.005) and heart rate (r = −0.99, P = 0.004), as well as direct correlations of LVPWT in diastole with the body weight at birth (r = 0.99, P = 0.005) and pulse rate (r = 0.99, P = 0.004).

Table 3: Parameters of the activity of intracellular markers of myocardiocytes in the blood serum of patients from the clinical groups of comparison (M±m)

Clinical groups and subgroups	Activity of intracellular enzymes (UN/L)		
	LDG	CPK-MB	AST
513.08±59.39	55.61±4.79	59.64±8.24	
510.76±49.59	64.81±8.01	45.77±5.34	
569.08±66.95	64.81±11.73	44.07±5.49	
416.56±66.51	64.81±9.52	48.26±10.70	
>0.05	>0.05	>0.05	

Pt: Student criterion, LDG: Lactate dehydrogenase, CPK: Creatine phosphokinase, AST: Aspartate aminotransferase, MB: Myocardial band

On this basis, worse adaptation at birth, necessity to conduct cardiac-pulmonary resuscitation measures, longer period of administration of inotropic drugs in the 1st days of life of preterm neonates could influence upon the results of their echocardiographic examination. Thus, inotropic support in the maternity home during 3 days and longer was given to a third (30.8%) patients with the term of gestation <32 weeks, every fifth preterm infant (20.6%) and only 8.7% of neonates from I clinical group. Although concerning term neonates from I group, the chances of long (≥3 days) inotropic support increased inconsiderably in patients from IIB subgroup: OR–4.67 (95% CI 2.07–10.55), RR–1.81 (95% CI 1.0–3.64), AR = 0.35; and representatives from II group: OR–2.72 (95% CI 1.17–6.36), RR–1.51 (95% CI 0.71–3.18), AR = 0.24.

At the same time, the conducted correlation analysis demonstrated that in the group of preterm neonates the results of EF possessed a reverse correlation with Apgar score at the 1st min of life (r = −0.43, P = 0.016) and at the 5th min of life (r = −0.43, P = 0.017). However, direct correlation of EF was determined by cardiac-pulmonary resuscitation measures in the delivery room (r = 0.64, P = 0.0001), the period of administration of inotropic drugs (r = 0.68, P = 0.04), and for SF with severity of general condition disorders at birth (r = 0.36, P = 0.05) and artificial respiration performed (r = 0.39, P = 0.03).

Conclusions

Analysis of clinical-anamnestic findings determined that term males suffer from NS reliably more frequent which is clearly associated with the risk of NS development. Increase of CPK-MB serum activity can be considered as a sign of

Table 4: Comparative average results of echocardiography of children from the clinical groups (P±m)

ECG parameter	Groups and subgroups of patients				Pt
	I (n=23)	II (n=34)	IIA (n=21)	IIB (n=13)	
EF (%)	74.22±1.46	77.90±0.94*	77.19±1.24	79.4±1.27*	I:II,IIA* <0.05
SF (%)	38.68±1.12	39.58±0.61	39.05±0.68	40.70±1.20	>0.05
EDV (mm)	17.2±0.40	15.12±0.32*	15.66±0.36*	14.16±0.54*,**	I:II, IIA, IIB* <0.05 IIA: IIB** <0.05
LAD in diastole	9.0±0.21	8.17±0.09*	8.23±0.11*	8.07±0.14*	I:II, IIA, IIB* <0.05
LVPWT in diastole	3.1±0.07	2.85±0.06*	2.89±0.06*	2.77±0.12*	I:II, IIA, IIB* <0.05

EF: Ejection fraction, SF: Shortening fraction, EDV: End-diastolic volume, LAD in diastole: Left atrial diameter in diastole, LVPWT in diastole: Left ventricular posterior wall thickness in diastole, Pt: Student criterion, ECG: Echocardiography, *P<0.05 I:II, ** P<0.05 IIA:IIB myocardial dysfunction development caused by NS. The analysis of echocardiographic parameters conducted in the group or preterm neonates found a direct correlation of the EF with initiation of cardiovascular resuscitation immediately after birth and the period of introduction of inotropic drugs.

Data and materials availability

All the data associated with this study are present in the paper.

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Conflicts of interest

There are no conflicts of interest.

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