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Newborn autopsies: experience of referral level III neonatal intensive care unit in Turkey

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Abstract

Objective: Neonatal autopsies are a guide to explore the causes of the perinatal mortalities which is important marker for evaluation of the health policies. Multidisciplinary approach which includes obstetrician, pediatrician, pathologist and geneticist is required for the neonatal autopsies. In our study, we have examined the significance of neonatal autopsy in neonatal deaths occurred in our clinic within 2 years, and analyzed whether neonatal autopsy has any impact on confirming and/or modifying reason of death.

Methods: Thirty-eight neonatal autopsies between January 2009 and December 2010 were evaluated in respect to demographic characteristics, clinical and pathological diagnosis retrospectively.

Results: Totally 7055 neonates were hospitalized in our neonatal intensive care unit between January 2009 and December 2010. Among them, 404 of the neonates passed away (5.7%). Only 38 (9.4%) of the neonates' parents gave permission for autopsy. Fifteen of these neonates were female (39%) and 23 of them were male (61%). Sixty percent of these neonates were premature. Prematurity was higher in male neonates (p=0.001). Median week of gestation was 32 (22-41). Median overall survival of the neonates were 4 (0-80) days. When compared according to gender, there was statistically no significant difference between survival periods. Prematurity rate was quite high among male neonates (p=0.001). Eighty-three percent of the clinical diagnoses were correlated with the pathological diagnosis. Sixty percent of the clinical and pathological diagnoses were cardiovascular anomalies, diaphragmatic hernia, perinatal asphyxia and prematurity. Two neonates had pneumonia diagnosis by the autopsy. Only one of these cases had chorioamnionitis in the placenta.

Conclusion: Neonatal autopsy rates should be increased to decrease the neonatal mortality rate in our country. Neonatal autopsies should be done with multidisciplinary approach and become prevalent and get more progress in our country.

Key words: Newborn autopsies, mortality, intensive care.

Yenidoğan otopsileri: Tek merkez deneyimi

Amaç: Yenidoğan otopsileri, sağlık politikalarının değerlendirilmesinde önemli olan perinatal mortalitenin sebeplerinin belirlenmesinde yol göstericidir. Yenidoğan otopsisi, kadın doğum ve klinik genetik uzmanı, pediatrist ve patologdan oluşan bir ekip işidir. Çalışmamızda, ünitemizde 2 yıllık süreçte meydana gelen neonatal ölümlerde yenidoğan otopsisinin yeri, otopsinin, ölüm nedenini kesinleştirme ve/veya değiştirmede etkili olup olmadığı incelenmiştir.

Yöntem: Ünitemizde Ocak 2009 - Aralık 2010 tarihleri arasında otopsi izni alınan 38 hastanın demografik özellikleri, klinik ve patolojik tanıları retrospektif olarak incelendi.

Bulgular: Belirtilen tarihler arasında 7055 hasta yenidoğan yoğun bakım ünitesine yatırılmış, 404 hasta kaybedilmiş (%5.7) ve bunların 38'inden (%9.4) otopsi izni alınmıştır. Bu hastaların 15'i (%39) kız, 23'ü (%61) erkekti. Otopsi yapılan yenidoğanların %60'ı prematüre idi. Hastaların ortanca gebelik haftası 32 (22-41) hafta bulundu. Hastaların ortanca ölüm süresi 4 (0-80) gün idi. Cinsiyete göre gruplandırıldığında ölüm süresi arasında istatistiksel anlamlı bir fark saptanmadı. Erkek bebeklerde prematürite oranı belirgin olarak yüksekti (p=0.001). Klinik tanı patolojik tanı ile %83 oranında uyumlu idi. Klinik ve patolojik tanıların %60'ını kardiyovasküler anomali, diyafram hernisi, perinatal asfiksi ve prematürite oluşturmakta idi. Otopsi ile 2 olguda pnömoni tanısı konuldu. Bu olguların sadece birinin plasentasında koryoamniyonit tespit edildi.

Sonuç: Ülkemizde neonatal mortalitenin düşürülmesi için neonatal otopsi oranları arttırılmalı, neonatal otopsinin ülke genelinde yaygınlaşması için ekip çalışması yönündeki eğilimlerin yaygınlaştırılması ve geliştirilmesi gereklidir.

Anahtar sözcükler: Yenidoğan otopsileri, mortailite, yoğun bakım.

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Introduction

The word autopsy is formed of 'autos' which means 'self' and 'opsis' which means 'view'. It briefly means the act of seeing with one's own eyes. Autopsy contributes to detect reason of death and to confirm diagnoses unknown previously, to understand new diseases, and to establish efficiency and reliability of new diagnostic and therapeutic approaches of clinical diagnosis. Its contribution to public health statistics and training is indisputable. Newborn autopsy provides very valuable information for offering consultancy to parents who lose their babies. Also, showing actual reason of death by autopsy may relieve the guilt feelings of parents due to maternal diseases or medication. Perinatal autopsy is obligatory for learning actual reason of death and follow-up next pregnancies of individual. Basic reason of such examinations is to determine the recurrence risk of event and to guide prenatal diagnosis and follow-up for next pregnancies addition to find actual reason of death.

By the studies performed, it has been shown that the data obtained by perinatal autopsy is able to change 22-76% of clinical diagnoses, 40% of estimated recurrence risk, 9% of preconceptional care recommendations, 21% of prenatal diagnostic procedures, 7% of prenatal management, and 3% of neonatal management.[1] Despite the advanced modern clinical researches, autopsy has been modifying 30% of antemortem misdiagnoses.[2] It has been shown in the study performed by Kumar et al. that neonatal autopsy gives a chance for new diagnosis at a rate of 44%.[3] Some particular pathologic diagnosis in perinatal autopsy has a role to give clue for diagnosing specific diseases. For example, when intraluminal calcifying meconium may indicate trisomy 21, intestinal atresia or cystic fibrosis, cardiac rhabdomyoma may indicate tuberous sclerosis, myocardial infarct, and secondary calcifying focus may indicate trisomy 21 or 13.

In our study, we have examined the significance of neonatal autopsy in neonatal deaths occurred in our clinic within 2 years, and analyzed whether neonatal autopsy has any impact on confirming and/or modifying reason of death.

Method

Demographic data, and clinical and pathologic diagnoses of 38 neonates with autopsy permission were examined retrospectively between January 2009 and December 2010.

Results

Totally 7055 neonates were hospitalized in our neonatal intensive care unit between January 2009 and December 2010, 404 of them passed away (5.7% mortality) and autopsy permission was obtained for 38 of them (9.4%). While 15 of them were female (39.4%), 23 of them were male (60.6%). Sixty percent of these neonates were premature. Median week of gestation was found to be 32 (22-41). Median overall survival of the neonates were 4 (0-80) days. When compared according to gender, there was statistically no significant difference between survival periods. Prematurity rate was quite high among male neonates (94% vs. 33%; p=0.001).

The correlation of clinical diagnosis with pathologic diagnosis was 83.3%. Sixty percent of the clinical and pathological diagnoses were cardiovascular anomalies (CVS), diaphragmatic hernia, perinatal asphyxia and prematurity. The most frequent diagnoses were CVS anomaly in 4 cases, diaphragmatic hernia in 2 cases, and perinatal asphyxia in 2 cases. The most frequent secondary diagnosis accompanying the reason of death was prematurity, while the most frequent pathologic new diagnosis was pneumonia in 2 cases. Autopsy results and characteristics are listed in **Table 1.**

Discussion

Death at neonatal period may depend on many reasons. Metabolic diseases such as disorders of long chain fatty acid metabolism may cause sudden infant deaths in the very first days of life. This disease can be defined by checking carnitine/acylcarnitine profile in Guthrie sample or showing increased chylomicron in liver or heart tissue to be taken in no time, and DNA may be extracted from these samples. Therefore, sample should be taken to Guthrie card in newborn deaths. Routine autopsy diagnosis of metabolic diseases is nonspecific. No diagnosis is established during autopsy except the diagnoses coherent with sepsis in many cases. There is no way to establish diagnosis other than taking samples just before or after death. In fact, it is recommended to inform family about deterioration, and to ask permission for biopsy and even autopsy before baby is lost. Even though such permission cannot be obtained, it is significant to get required samples for diagnosis: blood sample to be taken onto Guthrie card, blood sample, plasma or serum sample to be taken into tube with EDTA, and sterile urine sample.

Table 1. Characteristics of autopsy cases.

Autopsy number	38
Delivery week	32 (22-41)
Birth weight	1685 (436-3330)
Gender (F/M)	15 (%39.4) / 23 (%60.6)
Median death day	4 (0-80)
Maternal age	27 (20-36)
Coherence rate of clinical diagnosis - autopsy diagnosis	32/38
Prematurity in diagnosis	
Available	23/38 (%60)
N/A	15/38 (%40)
Anomaly in diagnosis	
Available	17/38 (%44.7)
N/A	21/38 (%55.3)
CNS anomaly in diagnosis	
Available	2/38 (%5.2)
N/A	36/38 (%84.8)
CVS anomaly in diagnosis	
Available	4/38 (%10.4)
N/A	34/38 (%89.6)

CNS: Central nervous system, **CVS:** Cardiovascular system.

Skin biopsy, and if possible, muscle and liver, brain and heart muscle tissue samples to culture are very helpful for diagnosis.

The medical history which is very significant in pediatric approach also has a serious impact on neonatal autopsy results. Ethnical origin, consanguinity background, maternal diseases, and previous pregnancy history enlighten diseases to be researched. For instance, the deficiency of long chain 3-OH acyl coenzyme A in fetus causes HELLP syndrome, acute hepatic lipidosis, and persistent emesis in pregnant woman. As another example, steroid sulfatase deficiency causes prolonged labor since it is the reason of decreased placental estrogen production. Oligohydramnios and polyhydramniosis histories are also helpful to detect pathology in fetus.

Photographing postmortem patient also helps to diagnose. Not only abnormal findings but also normal findings can be helpful. For example, pictures showing the presence of normal nails and normal fingers may help to rule out many syndromes.

Although direct postmortem radiological imaging may provide very detailed data, it is frequently overlooked in Turkey. However, by the imaging, gestational age can be guessed by checking ossifications, it becomes possible to determine fractures (if any) and their timings, and significant data can be obtained by determining abnormal gas flatulency and calcifications in extra-osseous organs (i.e. meconium peritonitis, hepatic, adrenal calcification). The radiography to be performed should include entire anteroposterior-lateral body, head should be positioned straight, nose should be aligned with umbilicus and upper and lower limbs should be in anatomical position. Kalifa et al. showed in their study that postmortem direct imaging provided significant data at the rate of 13.5%, and additional data at the rate of 34.5%.[4] Gronvall and Graem stated that abnormalities were detected at a rate of %59 by direct graphies.[5] It is recommended to do radiological imaging, if possible, in cases where autopsy is especially refused.[6]

Also, many new methods have been discussed for cases where autopsy is impossible. There are on-going studies on needle autopsy, endoscopic autopsy, ultrasonographic autopsy (echopsy), verbal autopsy and magnetic resonance (MRI) autopsy.[7] Although MRI autopsy performed by postmortem MR imaging seems to be non-invasive and more advantageous than conventional autopsy for showing cranial pathologies, the golden standard is still the conventional autopsy,[8] because MRI autopsy is still insufficient for cardiac pathologies, and it has a high rate of false positivity since it detects intraventricular bleeding and hematomas which cannot be detected in conventional autopsy. Also, it does not allow performing histopathological examination.

One of the most significant reasons for low rates of autopsy is the difficulty to get autopsy permission. There are some reasons preventing to get autopsy permission. It was reported in a study performed that hospitalization is a significant factor, and that autopsy permission was obtained for 82% of those who survived 1 day or less, for 75% of those who survived longer than 3 months and for 52% of those who survived 2-92 days.[9] In another study, it was shown that number of autopsy permission obtained increases as postnatal age and hospitalization in intensive care unit increase.[10] It was also indicated that premortem diagnosis is significant. The rate of obtaining autopsy permission for babies with asphyxia diagnosis was two times higher

than those with cardiac pathology.[9] Another significant factor is doctor who attempts to obtain permission. It was reported that a doctor who is in a consultant position or performs follow-up of baby continuously has a higher rate to get the permission.[9] Also, doctors sometimes have hesitations for asking autopsy permission. There are three reasons: not being a perinatal pathologist, not to upset family anymore, or the necessity to ask signing another informed consent form. Another reason for the hesitation is the concern that autopsy result may cause to question clinical judgments.[11]

Religious beliefs also have a significant impact on autopsy permissions. In Turkey, 88.7% of the population defines themselves as Muslim. In Islam, a voluntary autopsy cannot be allowed since it is believed that autopsy ruins the body and makes it ugly. Also Islam advises to bury dead bodies before sunset, and it is thought that autopsy may delay the burial.[12] According to Islam, death is the will of Allah and is a natural part of life, so autopsy can be seen as necessary.[13] Besides, it is stated that hurting dead one is equivalent to hurt living one.[14] Special procedures are required to prepare body for the life after death, and it is thought that autopsy may ruin such preparations.[13] Since Islam advises to bury dead bodies in a short time, a Muslim family should be assured when asking for autopsy permission that autopsy will be done timely.[15] Also, informing family that the body will be buried intact, and that internal organs can be replaced after examination may help to obtain autopsy permission easily.[12] Family should be communicated well; communication with spouse who is head of family or the oldest individual in family may help to communicate for autopsy permission.[12,14] Additionally, during decision making, family can discuss with an Islamic scholar or imam.[14] Islam does not allow tormenting dead ones; so, family should be informed that such torment will not occur, and advantages of autopsy should be communicated.

Autopsy form of all patients with obtained autopsy permission should be filled completely, death certificates should be completed properly in all infant deaths, and information form for perinatal and neonatal deaths should be filled as reason of death includes a single diagnosis.

Ideally, newborn autopsy is performed by a perinatal pathologist. However, even though pathologist is very experienced and well-educated, briefing by clinician changes the result and quality of autopsy distinctly. Sharing medical history of patient and mother, laboratory and imaging results, rare findings in patient, and negative and positive findings about diagnoses considered by clinician may guide autopsy. If required, slide, photograph, radiological findings, and consultation results should be reported to pathologist.

The method to be followed during autopsy may vary according to birth weight, being term or preterm, and presence of anomaly or hydrops in case (**Fig. 1**). No matter what method is followed by pathologist, it is important to remember that placenta is also a fetal organ and should be examined in detail. It provides significant information about prenatal period, and also postnatal prognosis and late phase diseases.[16-18] For example, presence of non-occlusive mural thrombus is associated with increased fetal thromboembolic complication risk in term baby.[19] Chorionic villus edema detected before any particular chorionic vasculitis is associated with increased cerebral palsy and decreased neurological function risk in babies with extremely low birth weight. Naeye et al. associated chorionic villus edema with increased mortality and morbidity in preterm babies, and reported that it can be the indicator of decreased fetal cardiac functions.[20] In another study, acute chorioamnionitis was associated with low scores of childhood cognitive tests.[21] Also, very important placental findings showing whether fetal ischemia is chronic or acute are especially helpful for forensic cases.[22] Moreover, when autolysis occurs in stillbirth cases, the most appropriate location for karyotype analysis is placenta. In placenta examination, cord length and blood vessel number is important. For example, a short cord indicates a neuromuscular disease while long cord indicates heart failure, and changes in blood vessel number indicates concomitant anomalies. A swab culture to be taken from placenta by stripping corio is a suitable medium for generating microorganisms which are the reason of death. It has been shown that the cells on fetal part of placenta may survive a few weeks even after death of fetus. When required, karyotyping can be carried out by taking biopsy under sterile conditions from fetal membrane or chorion. Consequently, placenta is a fetal organ and an essential part of autopsy. In addition to placenta, cord examination in stillbirths is recommended particularly.[23]

Congenital anomalies are the reason of a significant part of deaths during perinatal period. Most of the congenital anomalies are caused by chromosomal abnor-

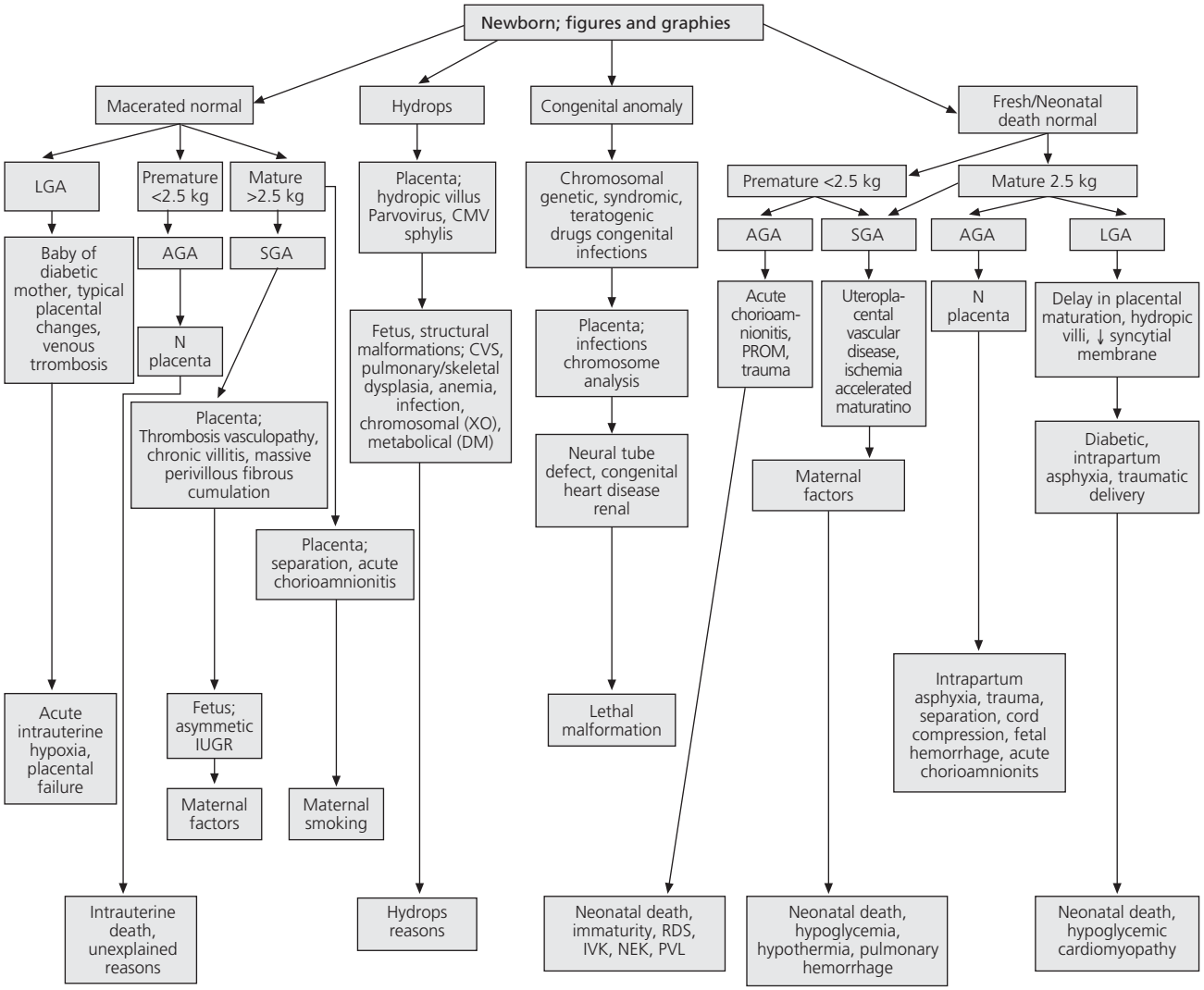

Fig. 1. The method to be followed in newborn autopsy.

AGA: appropriate for gestational age, **CMV:** cytomegalovirus, **CVS:** cardiovasculsr system, **DM:** diabetes mellitus, **IUGR:** intrauterine growth restriction, **IVG:** intraventricular bleeding, **LGA:** large for gestational age, **N:** normal, **NEC:** necrotizing enterocolitis, **PROM:** premature rupture of membranes, **PVL:** periventricular leukomalacia, **RDS:** respiratory distress syndrome, **SGA:** small for gestational age.

malities or are a part of a syndrome. Especially in these cases, information to be obtained by autopsy or chromosome study is quite essential and required to determine the recurrence risk and to follow up next pregnancies. When a genetic disease is considered, patient should be examined by genetic expert when alive and tissue sample should be reserved. If this is not possible, genetic expert should be consulted during autopsy. If patient has skeletal dysplasia or craniosynostosis, tissue should be retained for karyotyping and DNA study, and long bone should be frozen if possible. If arthrogryposis is present, karyotyping, muscle and spinal cord biopsy should be planned, and skin and muscle tissue should be retained. If patient has renal anomaly, urine analysis and karyotyping should be performed, and skin or renal tissue should be frozen. If congenital metabolic disease is suspected, gall sample, skin, brain, muscle and liver tissues should be retained. If a baby with hydrops fetalis dies before examinations are performed, appropriate samples should be taken immediately for hemogram, peripheral smear, blood type, viral culture and karyotyping.

Cytogenetic study should be conducted if patient has clinical suspicion, mother has 3rd loss, and there are non-immune hydrops fetalis, serious growth failure, there are more than two anomalies, a particular specific anomaly exists (i.e. complete atrioventricular canal defect), mother or father has known translocation, and if abnormal amniocentesis karyotype is detected.

Although progress has been made in pathological procedures such as immunohistochemistry, electron microscope, there has been a serious decline in newborn autopsy rates during the last decade. In a study performed, this rate has decreased from 71.2% (1984-1988) to 47.7% (1989-1993) in the USA.[3] This can be associated with various reasons. Increase in trust to imaging methods, actions for compensation, and lack of communication between pathologist and clinician may cause these reasons.[24,26]

In the study performed by Feria-Kaiser et al., two thirds of neonatal autopsies are congenital cardiopathy, prematurity, congenital syndromes and respiratory distress syndrome diagnoses .[27] In the study carried out on neonatal autopsies by Özkınay et al., it was observed that lethal anomalies (21%) in fetal autopsies are the second most frequent fetal death reason after asphyxia, while lethal anomalies in neonatal autopsies are the second most frequent fetal death reason after issued associated with prematurity and immaturity.[28] In our study, 60% of newborns autopsied were premature and anomalies were present in 44.7% of them. We consider the reason as our center is perinatology reference center.

Özdemir et al.[29] reported by their study that there was no change in diagnosis of 25 cases (73.5%) after autopsy, there were additional findings in 4 cases (11.7%), that diagnosis was changed in 4 cases (11.7%), and diagnosis was completely discordant in one case (2.9%). In our study, 83.3% of the clinical diagnoses were correlated with the pathological diagnosis; in 2 (5.2%) cases, diagnosis was changed completely.

Conclusion

Perinatal mortality rate is an inseperable part of common health policy of the country, and it is an essential criterion to evaluate the efficiency of primary pediatric health services in the society, and to compare with other countries. In perinatal deaths, autopsy should be carried out in order to examine the actual reason of deaths, to scrutinize the accuracy of clinical interpretation considered as death reason and to determine congenital anomalies. Multidisciplinary approach which includes obstetrician, pediatrician, pathologist and geneticist is required for the perinatal autopsies. Within a team work, obstetrician should provide detailed information about the follow-up and delivery, and pediatrician should provide detailed information about neonatal history. When required during autopsy, clinical geneticist should examine infant before autopsy and work with pathologist for syndrome considered. Normal and abnormal conditions should be documented, and anomalies which are hard to express verbally should be photographed. Full body radiography (lateral and anteroposterior) should be a routine part of the autopsy. Karyotype examination may be helpful in those with malformation, intrauterine growth retardation, maternal anamnesis, and fetal loss anamnesis in previous pregnancies. In fetal deaths, and in neonatal deaths if possible, placenta and cord should certainly be examined histologically. Autopsy is still of great value for final diagnosis and confirming diagnosis.

Conflicts of Interest: No conflicts declared.

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