Original Article

Ultrasound as screening modality in management of fever cases in dengue epidemic: Study of 202 cases

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Abstract

Aims and Background: Ultrasound is a screening procedure in suspected dengue fevers (DFs) and other febrile illness in epidemic areas with limited laboratory resources to help in prioritizing patients for emergency critical care. DF has become epidemic in India. Symptomatic dengue infection with any of the four serotypes of dengue virus can produce systemic and dynamic disease with a broad spectrum of illness with severe and nonsevere clinical manifestations.

Subjects and Methods: A retrospective record-based study of 202 cases of suspected DFs were evaluated by ultrasound for a period of 18 months during epidemic in Radiology Department. All age groups were included in the study. Ultrasound of abdomen and chest performed in between 3rd and 10th day of fever. The data compiled by incorporating sonographic findings, clinical findings, and laboratory results. Laboratory data include serology and platelet count.

Results: Ultrasound findings were analyzed, in comparison with clinical detection and laboratory results. Eighty-five percent were pediatric age group. The triad of ultrasound findings is stratified gallbladder wall thickening, 85.2%; ascites, 78%; and pleural effusions, 67.8%. Others are pericardial effusion 2.5%, hepatomegaly 9.1%, and splenomegaly 6.1%. Nearly 18.8% of severe dengue cases were observed. Detection of capillary leakage was 100% on ultrasound and 39.70% on thrombocytopenia. Eighty-six serology positive, 107 with no serology, and 6 seronegative cases were positive for ultrasound. Fifty-five percent isolated gallbladder edema is seen before thrombocytopenia.

Conclusion: Ultrasound can be utilized as the mainstay of investigation in epidemic regions with infrastructure shortage. Early demonstration of serosal collection helps to grade DF to severe dengue and prioritize patients for critical care.

Keywords: Dengue fever, dengue hemorrhagic fever, serology, severe dengue, thrombocytopenia, ultrasound, warning signs

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INTRODUCTION

Dengue is a mosquito-borne viral disease transmitted by female mosquitoes *Aedes aegypti*. Dengue fever (DF) has become epidemic in India from July to November, with increase during the rainy months. The most severe presentations are in children than in adults.[1] Dengue infection with any of the four serotypes of DV (DEN-1, DEN-2, DEN-3, and DEN-4) can produce systemic and dynamic disease with broad spectrum illness. Illness starts abruptly after incubation period and is followed

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by febrile, critical, and recovery phases. The severity of the disease is often called critical phase. In early febrile phase, the differential diagnoses are mostly from viral, bacterial, and protozoal infections. The World Health Organization/National Notifiable Diseases Surveillance System (WHO/NNDSS) case definitions are utilized for classification, and usage of the 2012 classification into dengue with or without warning signs and severe dengue has been suggested by the WHO for a triage of patients.[2] During the epidemic, the management of cases at public hospitals gets worse, and serological confirmation and virus isolation are not routinely performed due to logistic and cost reasons in epidemic situation.[3]

Only those patients who need emergency medical attention need to be monitored for capillary leakage and to be treated with appropriate fluids. It is found that the WHO classification system was not much in agreement by physicians, who were inclined to classify DF and dengue hemorrhagic fever (DHF) with evidence of plasma leakage even in the absence of both thrombocytopenia and a hemorrhagic tendency.[4] Colbert[5] recent studies have shown that the distinction between DF and DHF is not sufficient in some patients as per the WHO criteria. There has been a paucity of data regarding the usefulness of sonography for triage of dengue patients on WHO parameters.[6]

Sonography findings included are gallbladder (GB) wall thickening, pleural effusion, ascites, pericardial effusion, and organomegaly in favor of warning signs and severe dengue. Although findings are variable and nonspecific, early detection will help in management and for differential diagnosis of other febrile diseases.[7]

The aim and objectives of this study was to make use of Ultrasound to screen all febrile cases during dengue epidemic to detect warning signs characteristic to dengue fever for early management to reduce mortality especially in public hospitals with limited laboratory resources and infrastructure.

SUBJECTS AND METHODS

It is a retrospective, record-based study conducted in the Department of Radiology, Government General Hospital, Anantapur, Andhra Pradesh, India. Two hundred and two cases were selectively collected under the definition of presumptive DF in the period of 18 months, during epidemic outbreak from June 2014 to December 2015 with a peak between August and October and ongoing cases throughout the year. Case classification utilized as suspected, probable, and confirmed cases of dengue as per WHO/NIDDM, described as (1) suspected dengue which is compatible with clinical definition, (2) probable dengue compatible with clinical definition and either positive serology or with epidemic linkage, and (3) confirmed case is compatible with clinical definition and with laboratory confirmation.

The other fevers/febrile illness excluded depending on laboratory tests such as malaria, widal positive cases, and also viral hepatitis with no epidemic linkage. All age groups of patients are included, more number being pediatric age group. All patients referred for ultrasound scan of chest and abdomen for evaluation of fever, with symptoms of pain abdomen, shock, hemorrhagic manifestations, and pain in the right hypochondrium. The data compiled by incorporating, sonographic findings, clinical findings, and laboratory results. Complete medical history of symptoms and signs is recorded from case sheets and with emphasis on their residential address for epidemiologic linkage. Laboratory data include serology comprised IgM, IgG antibodies, NS_1 Ag, and platelet count. Other laboratory tests include complete blood picture, liver function tests, and tests for malaria parasite and for enteric fever. Results are obtained from laboratory blood analysis. Cases were also grouped based on serology results as serology positive, serology negative, and probable dengue with no serology results available, and they were correlated with ultrasound positivity and platelet count at <150,000 and <100,000 cells/μl.

Ultrasound scans were done under high-end Esaote class C machine using convex and high-frequency linear probe. Abdominal and chest scan was performed by both probes simultaneously to detect even minimal leakage of fluid into serous cavities. GB wall thickness more than 3 mm was considered and measured on the anterior subhepatic wall in a longitudinal section. Ultrasound findings were statistically analyzed for establishing presumptive DF cases into 1, with or without sonographic warning signs of cavitary fluid collection and severe dengue cases with available laboratory results.

RESULTS

Of the 202 cases, 85% patients are in pediatric age group and others being 14.5%, the youngest being 4 months old. Most of them presented in-between 3rd and 10th day of fever and most of the cases were done on the 5th day of fever. The cases were categorized depending on (1) clinical features, (2) ultrasound findings, (3) clinical/ultrasound warning signs, (4) suspected severe dengue case analysis,

(5) positive scans in relation with availability of serology, (6) thrombocytopenia in relation with ultrasound and serology, and (7) isolated GB wall thickening.

Category 1: Clinical features

Fever was the presenting symptom in 198 cases (98%), followed by headache, skin rash, vomiting, and with other symptoms [Figure 1]. Four cases presented with pain abdomen without fever admitted in the surgical ward. Seven cases were presented with fever and bleeding manifestations such as hematuria, melena, and hematemesis. Based on clinical findings, 156 cases were labeled as presumptive/probable dengue, 13 cases with warning signs, and 33 cases as severe dengue based on WHO parameters.

Category 2: Ultrasound findings

The ultrasound findings were as follows [Figure 2]: increased GB wall thickness with stratification (85.2%), followed by ascites (78.0%) and pleural effusions and pericardial effusion (2.5%). Among (67.8%) pleural effusions, right-sided effusion (52.5%) is more common. Among organomegaly, hepatomegaly (9.1%) followed by splenomegaly (6.1%) was observed, and some patients have multiple scan findings.

Category 3: Clinical and laboratory warning signs

The following findings are clinical and laboratory warning signs of dengue based on the WHO criteria.

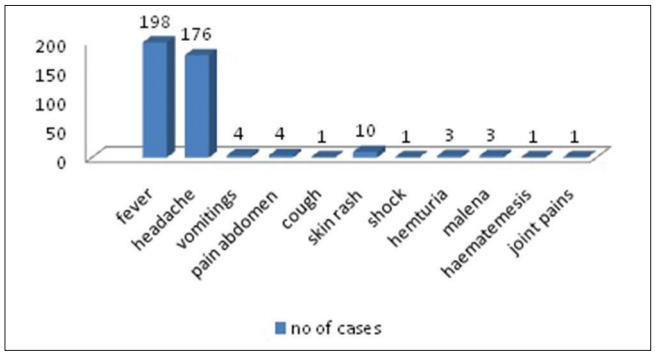

Figure 1: Clinical features in 202 cases

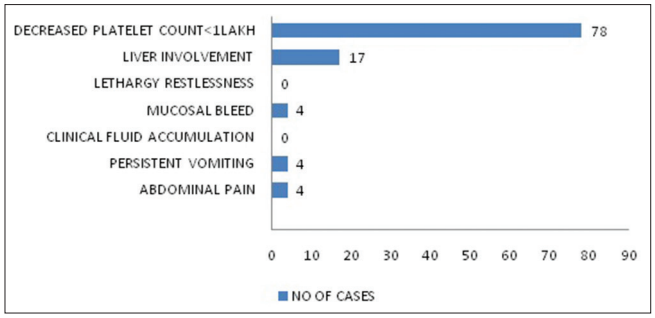

Figure 3: Clinical and laboratory warning signs in our study

As given in Figure 3, serosal fluid accumulation, one of the important clinical warning signs, was not identified clinically in our study. In 196 cases (97%), detection of serosal fluid collection was done on ultrasound considered as ultrasound warning sign in presumptive cases, when compared with combined clinical and laboratory findings which are 52.9% [Figure 3].

Category 4: Suspected severe dengue case analysis

Analysis of 37 suspected severe dengue cases was done on ultrasound findings, platelet count, and serology as shown in Table 1.

Category 5 and 6: Positive scans in relation with serology and thrombocytopenia

Percentage of positive scans correlated with serological data and platelet count in percentage and depicted in Figure 4. All serology positive cases and 107 serology not available cases revealed 100% positive ultrasound with serosal fluid collections. Seven cases negative for NS1, IgG, and IgM, resulted in six positive ultrasounds suggesting the possibility of other febrile illness of dengue mimics. Thrombocytopenia of <100,000 cells/μl was analyzed in relation with serology and positive scans and shown in Figure 4.

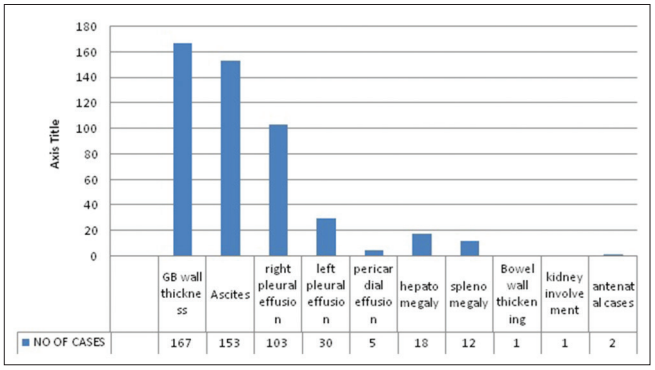

Figure 2: Ultrasound findings in 196 cases

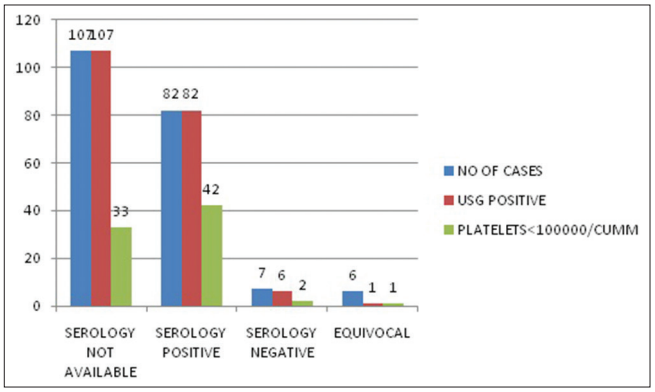

Figure 4: Serology in relation to positive scans and platelets

Table 1: Severe dengue analysis in 37 cases

Organ involvement on ultrasound	*n* (%)	Platelets			Serology		
		>100,000 (cells/μl) (%)	<100,000 (cells/μl) (%)	<50,000 (cells/μl) (%)	Positive (%)	Negative	Not available (%)
Liver	17 (45.9)	14 (37.8)	14 (37.8)	9 (24.3)	20 (54)	-	17 (46)
Spleen	10 (27)						
Pericardial effusion	5 (13.5)						
Lung	1 (2.7)						
Kidney	1 (2.7)						
Bowel	1 (2.7)						
Pregnancy	2 (5.4)						

Category 7: Isolated gallbladder wall thickening with serology and platelet count

GB wall thickening is the only scan finding in twenty cases after excluding other related causes and correlated with serology and platelet count. Among these cases, only 40% presented with thrombocytopenia of <150,000 cells/μl indicating the appearance of capillary leakage earlier to the appearance of thrombocytopenia in dengue cases.

DISCUSSION

Dengue is a complex disease with variable clinical picture in the early phase and often unrecognized or misdiagnosed as other fever causing in a tropical area. Although DF is a self-limited febrile illness, DHF is characterized by prominent hemorrhagic manifestations with thrombocytopenia, an increased vascular permeability, and is associated with a high mortality rate.[8] Following incubation period, patients present with sudden onset of fever which can remain for 2–7 days and is accompanied by symptoms such as headache, vomiting, myalgia, arthralgia, anorexia, sore throat, and a macular skin rash. It is during this period that differentiating dengue from other febrile diseases proves troublesome.[9] Underlying comorbidities such as pregnancy, infancy, old age, diabetes mellitus, and renal failure will complicate the natural course of illness.

The present study is to establish ultrasound role as a screening procedure in dengue epidemic outbreak in all probable DF cases. The main aim of the study is to evaluate ultrasound findings and correlating them with available clinical and laboratory data for early detection of fluid collection, a clinical warning sign, signaling the need of hospital care in areas with resource crunch of trained workforce and infrastructure.

The first assessment is the study of fever cases referred to the Department of Radiology for ultrasound are grouped as per the WHO guidelines and dengue virus infection 2015 Case definition by NNDSS,[10] as described earlier in subjects and methods. In our study, 98% of patients presented with fever and associated with headache, vomiting, skin rash, and with a history of epidemic linkage. Eighty-two cases presented with positive serology indicative of dengue infection and 33 cases referred to scan as severe dengue by clinical and laboratory findings. The second assessment was done based on identifying capillary leakage, a very important warning sign. Cases are grouped as with or without warning signs and severe dengue.

The various indirect clinical and laboratory evidences of capillary leak are such as hemoconcentration (>20%), hypoproteinemia, or by repeated clinical assessment to recognize plasma leakage/critical phase in DHF are compared with direct evidence of capillary leakage by ultrasound into serosal cavities. In literature, sonography was found to have the highest sensitivity and negative predictive value in detecting plasma leakage.[6] Moreover, the presence of pleural effusion and ascites on ultrasound indicates that the patient is already in the critical phase.[11] The next 24–48 hrs of the critical stage can be dangerous and needed proper medical care to reduce mortality.

In our study, ultrasound identified 97% of critical phase which was 49% on clinical findings alone. The reason for this discrepancy could be capillary leak was probably minimal to be detected clinically and usage of high-end machines with multifrequency probes small amount of fluid and localized collections can be easily detected. Ultrasound would be ideal in detecting plasma leakage even before it clinically manifests, and similar findings have been reported earlier from Indonesia.[7] We have reported 196 cases of positive ultrasound findings which are depicted in Figure 2. In our study, a maximum number of cases had ultrasound on the 5th day of fever in critical phase, correlated with Nair *et al*. study with a mean number of days at which the inpatients presented on 5.74 days.[12]

The common ultrasound findings are GB wall stratification, pleural effusion, ascites, pericardial effusion, and organomegaly. The most common finding in our study was increased GB wall thickness with wall stratification (85.7%). Venkata Sai *et al*.[13] in his study with early and late scans during illness found GB wall thickening as the initial finding (100%) followed by pleural effusion. GB wall abnormality which

was observed from 2nd day to 10th day of fever presented with various degrees of stratified pattern of GB wall edema in our study [Figure 5a-d]. Isolated GB wall thickening in twenty cases as seen in our study can be considered as early sign of critical phase even before platelet drops.

Incidence of ascites 78.5% in our study is more when compared with others and was observed from 2nd to 10th day of fever.

Thickening of the GB wall and ascites were detected less frequently (43% and 52%) in the study of Srikiatkhachorn *et al*.[14] in contrary to 86% and 76% in our study. However, application of high-resolution ultrasound, with multifrequency probe might have improved the detection of small collections with high sensitivity as in our case. Minimal fluid was detected in pelvic cavity in some DF, and other febrile cases may reflect mild local serosal inflammation occurring as a nonspecific reaction in febrile illness.[14] There are no isolated cases of ascites in our study, and it was always seen associated with either stratified GB wall or pleural effusions, and finding was correlated with other data to confirm it as an ultrasound warning sign. Locations of ascites in our study were in pelvis, flanks, and in Morison's pouch [Figure 6a-d]. In addition, the presence of fluid in perirenal space indicates severe presentation of DHF as per Thulkar *et al*.[15] which were also observed in our cases [Figure 6c].

Over half of DHF cases had all three ultrasound signs of plasma leakage: thickened GB wall, pleural effusion, and ascites in the study of Srikiatkhachorn *et al*.[14] and our study also observed the similar triad [Figure 7] as the common signs of plasma leakage.

Pleural effusion found in 67.8% in our cases and observed from 3rd to 10th day of fever. It is both unilateral and bilateral; bilateral effusion in 14.7% with right-sided

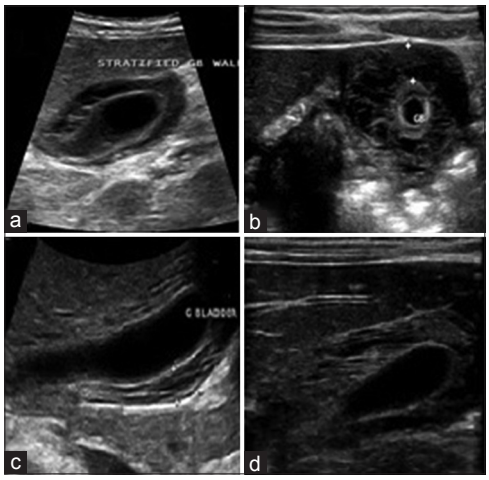

Figure 5: Longitudinal and transverse sections of GB demonstrating different degrees of patterns of stratified wall thickening with multiple echogenic layers intermingled with fluid

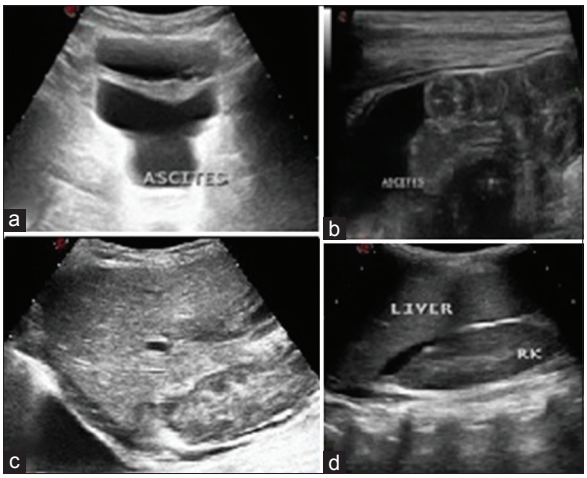

Figure 6: Ascites in (a) pelvis (retro-vesicle), (b) flanks, (c) sub diaphragmatic minimal perirenal, (d) morison's pouch

Figure 7: Ultrasound triad of dengue (GBwall thickening, pleural effusion and ascites)

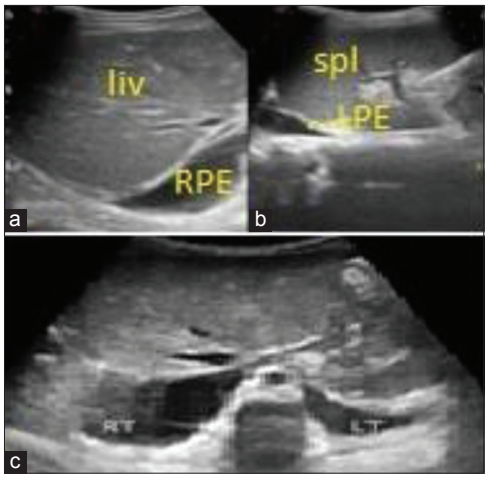

Figure 8: (a) Right pleural effusions; (b) Left pleural effusion and (c) Bilateral pleural effusions as ultrasound warning signs of capillary leakage

dominance (53%) [Figure 8a-c]. Venkata Sai *et al*.[13] also observed 71.87% right pleural effusion and 21.87% left pleural effusion, indicating less frequent left-sided effusions.

With signs of florid hemorrhage and shock, most of the severe dengue cases are identified clinically, and the role of ultrasound in such cases is further helpful to detect pleural effusion, pericardial effusions, and other organ involvement in support to clinical diagnosis.

In our study, 37 cases are categorized as severe dengue depending on ultrasound signs of pericardial effusion, organomegaly along with other findings [Table 1]. Among these 37 cases, NS1 is positive in 6, IgG in 8, IgM in 6 cases, and serology not available in 17 cases. Platelet count less than one Lakh was identified in 23 cases.

In 2.5% of cases, pericardial effusion was diagnosed [Figure 9] along with other signs of capillary leakage indicating severity of the disease. Ultrasound is sensitive to detect even a small quantity of pericardial effusion. Setiawan *et al*. could able to detect small pericardial effusions in 8% of severe dengue cases.[7] In our study, two antenatal cases identified as severe dengue with positive serology (IgM) with platelet count 40,000 cells/μl and bilateral pleural effusions, organomegaly on ultrasound. A high index of clinical suspicion is essential in any pregnant woman with fever during epidemics. Severe thrombocytopenia is the striking feature in 78% patients as observed in one study by Agrawal *et al*.[16] as in our case. Another case presented with menorrhagia, fever, and encephalopathy with NS1 positive and with platelet count <10,000 cells/μl. Computed tomography brain is normal and ultrasound scan of the abdomen on 5th day of fever has GB wall edema and ascites and considered as severe dengue. Another case of hematuria presented on the 5th day of fever with platelet count 30,000 cells/μl with positive IgG, ultrasound triad of plasma leakage, and splenomegaly, indicating severe dengue.

Chandak and Kumar[17] in her study about radiology role in early detection of DF found hepatosplenomegaly being the more common manifestation, which is contrary to our observation where the common triad of signs was in high incidence, might be due to more number of pediatric age group in our study as in the study of Venkata Sai *et al*.[13]

Although laboratory diagnosis is the gold standard for the diagnosis of dengue, results may not always be available in time to be clinically useful. A number of positive ultrasound cases in correlation with positive, negative, and nonavailable serological reports are summarized in Figure 4.

Figure 9: Ultrasound demonstrating pericardial effusion as an expression of plasma leakage in severe dengue

Table 2: Thrombocytopenia in 202 cases

Type of cases	>100,000 (cells/μl)	<100,000 (cells/μl)	<50,000 (cells/μl)	Number of cases
Serology				
Not available	74	20	13	107
Positive	40	30	12	82
Negative	5	2	0	7
Equivocal	5	0	1	6
Total	124	52	26	202

A number of thrombocytopenia cases are tabulated and figured in Table 2 and Figure 4. Thrombocytopenia arises from both decreased production of cells from bone marrow and an increased peripheral destruction of platelets, with a normal platelet count being 150,000–400,000 cells/μl.

In our study with 196 cases of positive ultrasound findings, thrombocytopenia (<100,000 cells/μl) was seen only in 39.7% cases, supporting literature stating that critical phase is only a surrogate marker for the period of rapid platelet drop. To summarize, ultrasound positivity is valued in epidemic regions irrespective of serological availability and platelet count in triaging the patients for emergency critical care.

Among various ultrasound examinations, high-resolution ultrasound appeared to be the most sensitive and yielded superior for detecting small fluid collection and minimal GB wall thickening. In our setup, frequent and continuous monitoring of patients and platelets is difficult due to cost-effectiveness and less workforce, where noninvasive and cost-effective procedure such as ultrasound can be utilized with more sensitivity during epidemics.

CONCLUSION

Ultrasound is the mainstay of investigation to detect capillary leakage when compared to the customary

methods, particularly in dengue epidemic, where there are limited laboratory resources and workforce crunch. This widely available noninvasive, easily accessible modality can be an immense help for prioritizing patients for intensive care units and can be supplemented by the use of the criteria for triage of dengue patients.

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Conflicts of interest

There are no conflicts of interest.

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