ULTRASOUND MEASUREMENT OF GALLBLADDER WALL THICKENING AS A DIAGNOSTIC TEST AND PROGNOSTIC INDICATOR FOR SEVERE DENGUE IN PEDIATRIC PATIENTS

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Abstract: Gallbladder wall thickening measured by ultrasound was significantly associated with severe dengue, as well as with hallmark features of thrombocytopenia and elevated hematocrit/hemoconcentration, in children with suspected dengue in Nicaragua. We demonstrate that gallbladder wall thickening serves as a clinically relevant diagnostic test and prognostic indicator of severe dengue in pediatric populations.

Key Words: dengue, dengue hemorrhagic fever, gallbladder wall thickening, ultrasound, prognostic indicator

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Approximately 2.5 to 3 billion people worldwide live in areas at risk for transmission of the mosquito-borne dengue flavivirus (DENV), and an estimated 100 million people worldwide are infected each year.[1] Clinical manifestations of the infection include dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). The classic symptoms of DF include high fever, headache, musculoskeletal pain, retro-orbital pain, and rash. The principal requirements for DHF classification are increased vascular permeability ("plasma leakage"), hemorrhagic manifestations, and thrombocytopenia (platelet count $\leq$100,000/mm^3); the additional presence of hypotension or narrow pulse pressure along with clinical signs of shock designates DSS.[2]

Ultrasound may be a promising alternative to radiography in support of dengue case management and triage in developing nations. As a prognostic indicator, ultrasound could potentially be used to assess which patients are at risk for entering the critical phase. Identifying these patients early could improve case management and outcome, as well as enable a more efficient allocation of hospital resources. Ultrasound allows detection of capillary leakage (eg, pleural effusion, ascites), as well as hepatomegaly, splenomegaly, and thickening of the gallbladder wall in patients with dengue. Recent studies of ultrasound in dengue patients have largely been confined to Asian regions where DHF predominates in hospitalized patients[3–6] and few have examined the relation of gallbladder wall thickening (GBWT) to clinical manifestations of severe dengue.

MATERIALS AND METHODS

Study Participants. The study was based in the Infectious Disease Unit of the Hospital Infantil Manuel de Jesús Rivera (HIMJR), the national pediatric reference hospital in Nicaragua, and included 73 children who presented to the HIMJR between August 2005 and February 2006 with clinical symptoms consistent with DF. Study participants included 37 females and 36 males, ranging in age from 5 months to 14 years old; with 16 patients aged $\leq$4 years, 26 patients aged 5 to 9 years, and 31 patients aged 10 to 14 years. The majority of children (58; 79%) were managed as inpatients, whereas 15

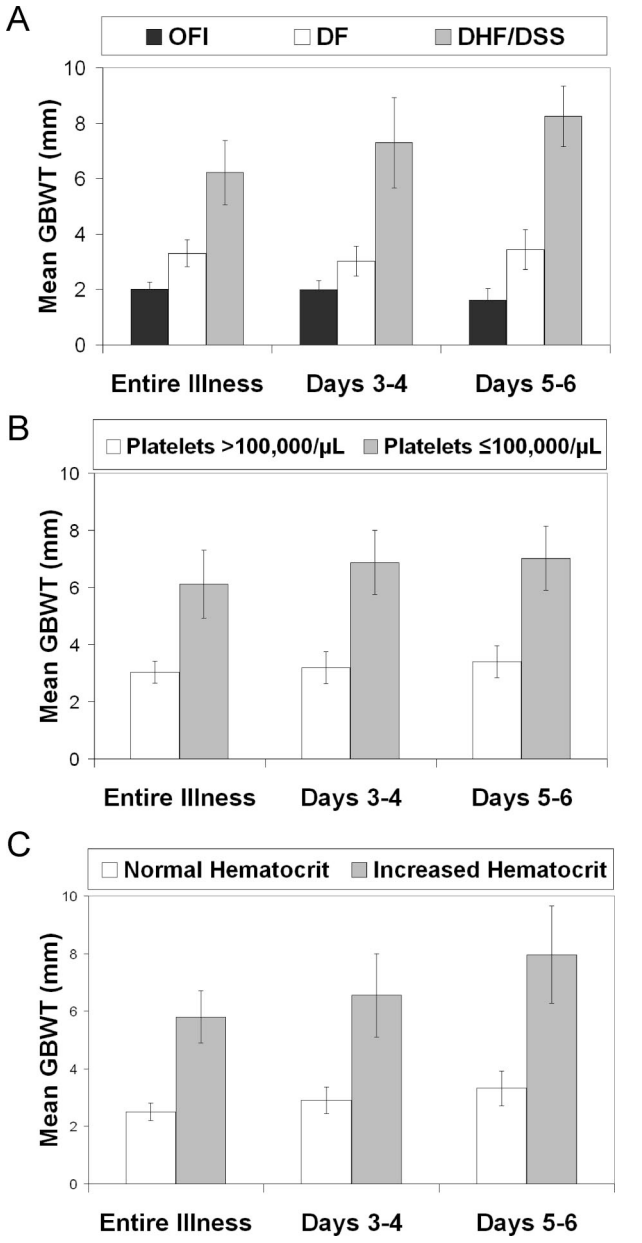

FIGURE 1. A, Differences in mean gallbladder wall thickening (GBWT) between children with nondengue febrile illness, dengue fever, and dengue hemorrhagic fever/dengue shock syndrome. Mean values were significantly different between the groups ($P <$ 0.01, multivariate analysis of variance); error bars indicate standard error of the mean. B, Differences in mean GBWT in relation to decreased platelet count. Mean GBWT measurements for each time period were compared with the platelet counts from that same time period. Mean values were significantly different between the 2 groups in each time period ($P < 0.01$, *t* test); error bars indicate standard error of the mean. C, Differences in mean GBWT in relation to increased hematocrit. Mean GBWT values for each time period were compared with the hematocrit/hemoconcentration measurements from that same time period. Increased hematocrit is defined as elevated hematocrit or hemoconcentration. Mean values were significantly different between the 2 groups in each time period ($P < 0.01$, *t* test); error bars indicate standard error of the mean.

(21%) were followed via daily outpatient visits. Eleven participants (15%) were diagnosed with DHF/DSS, 44 (60%) were confirmed as DF, and 18 (25%) were laboratory-negative for dengue, classified as other febrile illness (OFI). The serotype of dengue virus (DENV) was determined in 82% of positive cases, and DENV1 and DENV2 were identified in 9 (16.4%) and 36 (65.4%) cases, respectively.

During the course of their illness, patients received 1 to 5 ultrasounds (mean, 2.3) performed by RR using the GE Logitech Pro5 machine. Sonographic assessment included measurement of GBWT, pleural effusion, ascites, hepatomegaly, and splenomegaly. Increased hematocrit was defined as hematocrit ≥40 for children ≤2 years of age or hematocrit ≥42 for children >2 years, or hemoconcentration greater than or equal to 20% above baseline at discharge.

Serologic and virologic determination of DENV infection was performed at the National Virology Laboratory of the Ministry of Health in Managua. A positive case was indicated by IgM seroconversion, a 4-fold or greater increase in total anti-DENV antibodies as measured by Inhibition ELISA, detection of viral RNA by reverse transcription polymerase chain reaction, and or virus isolation.[7] Differentiation between DF and DHF/DSS was based on the World Health Organization criteria.[2]

Data Analysis. Data management was conducted using Microsoft Access, and data analysis was performed using STATA 9 (StataCorp LP, College Station, TX). Means were compared using multivariate analysis of variance procedures or one-sided *t* tests. Random-effects logistic regression analyses were used to compute the adjusted and unadjusted odds ratios. Receiver operating characteristic (ROC) analysis was performed to determine the optimal cutoff values.

Human Subjects Approval. This study was approved by the human subjects committees at UC Berkeley, Stanford University, the Nicaraguan Ministry of Health, the HIMJR, and the World Health Organization.

RESULTS

Of a total of 73 study participants, 55 (75%) were laboratory-confirmed as DENV infections, whereas 18 (25%) tested negative for dengue and were classified as OFI. Of those with confirmed DENV infection, 44 (80%) were classified as DF and 11 (20%) were diagnosed with DHF/DSS. Ultrasound-measured GBWT was found to be significantly different between all 3 subgroups of patients when adjusted for age and sex ($P < 0.01$). Patients with OFI had the lowest mean GBWT (2.00 mm), whereas DF patients had a mean GBWT of 3.31 mm, and patients with DHF/DSS displayed a mean GBWT of 6.21 mm (Fig. 1A). Differences in GBWT between the 3 patient groups was significant ($P < 0.01$) 3 to 4 days as well as 5 to 6 days postonset of symptoms.

To evaluate ultrasound GBWT as an indicator of DHF/DSS, a ROC analysis was performed using ultrasound results grouped by 2-day intervals postsymptom onset (Table 1). The area under the ROC curve for day 3 to 4 was 0.77 and for day 5 to 6 was 0.90. Best results were obtained with cutoff values of 4 and 5 mm GBWT. Sensitivity and specificity for 4 and 5 mm cutoff values on day 3 to 4 were 80.0% and 79.1%, and 80.0% and 86.1%, respectively. With a population prevalence of 19% DHF/DSS in our study, the positive predictive value, negative predictive value, and percentage correctly classified were 47.1%, 94.4%, and 79.3% for a cutoff of 4 mm, and 57.1%, 94.9%, and 84.9% for a 5 mm cutoff on days 3 to 4 postsymptom onset. Sensitivity and specificity on days 5 to 6 were 100.0% and 79.0% for a cutoff of 4 mm and 87.5% and 86.8% for a cutoff of 5 mm. Positive predictive value, negative predictive value, and percentage correctly classified were 50.0%, 100%, and 82.6% for a 4 mm cutoff and 58.3%, 97.1%, and 87.0% for a 5 mm cutoff on days 5 to 6. Although the mean GBWT differed significantly between children with dengue and OFI ($P = 0.01$), GBWT did not have high sensitivity/specificity as a diagnostic for DENV infection.

An increased GBWT also significantly correlated with decreased platelet count and increased hematocrit. Patients with low platelets (≤100,000 cells/mm^3) had a mean GBWT of 6.12 mm compared with 3.04 mm in those with normal platelet count ($P < 0.01$) (Fig. 1B). A random effects logistic regression analysis of GBWT cutoff values of 4 and 5 mm in relation to low platelet count yielded odds ratios of 20.1 (95% CI: 4.5–89.2) and 16.6 (4.9–56.4), respectively, when adjusted for age and sex. Similarly, mean GBWT in patients with elevated hematocrit/hemoconcentration was 5.80 mm compared with 2.51 mm in those without ($P < 0.01$) (Fig. 1C). Random effects logistic regression analysis showed that GBWT of ≥5 mm was significantly associated with increased hematocrit [OR: 5.7 (1.6–20.8)], whereas the same tendency was observed for a cutoff of ≥4 mm [OR: 3.0 (0.9–9.8)].

DISCUSSION

To our knowledge, this study is the first published report that uses ultrasound measurement of GBWT to differentiate between pediatric nondengue controls (OFI), classic DF, and DHF/DSS and to use ROC analysis to determine the optimal cutoff values for GBWT. Many studies have examined exclusively DHF patients[4,8,9] or do not differentiate between DF and DHF,[5] and importantly, do not include nondengue patients.[3,4,6,9–11]

Positive GBWT is often defined as greater than 3 mm[9,10,12]; yet, with regards to pediatric dengue in our study, we found more favorable sensitivity and specificity using values of ≥4 and ≥5 mm to differentiate DHF/DSS. Although the best sensitivity/specificity results were achieved on day 5 to 6 postonset of illness, GBWT was also promising as a prognostic test for severe dengue on day 3 or 4, the time before the onset of the critical phase. Significant differences were also found in GBWT between dengue-negative patients and

TABLE 1. Ultrasound-Measured Gall Bladder Wall Thickening as a Prognostic Test for Dengue Hemorrhagic Fever

	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive Predictive Value % (95% CI)	Negative Predictive Value % (95% CI)	Percent Correctly Classified
Day 3–4					
3 mm	80.0 (44.4–97.5)	62.8 (46.7–77.0)	33.3 (15.6–55.3)	93.1 (77.2–99.2)	66.0
4 mm	80.0 (44.4–97.5)	79.1 (64.0–90.0)	47.1 (23.0–72.2)	94.4 (81.3–99.3)	79.3
5 mm	80.0 (44.4–97.5)	86.0 (72.1–94.7)	57.1 (28.9–82.3)	94.9 (82.7–99.4)	84.9
Day 5–6					
3 mm	100.0 (63.1–100.0)	52.6 (35.8–69.0)	30.8 (14.3–51.8)	100.0 (83.2–100.0)	60.9
4 mm	100.0 (63.1–100.0)	79.0 (62.7–90.4)	50.0 (24.6–75.4)	100.0 (88.4–100.0)	82.6
5 mm	87.5 (47.4–99.7)	86.8 (71.9–95.6)	58.3 (27.7–84.8)	97.1 (84.7–99.9)	87.0

DF cases. Cutoff values of ≥4 and ≥5 mm were found to be optimal as both diagnostic and prognostic indicators DHF/DSS.

Few studies of ultrasound in dengue management have correlated results with other specific indicators of dengue severity. One study in Mexican adults examined several parameters and only found association of GBWT with ascites, not thrombocytopenia (hemoconcentration was not evaluated).[11] Balasubramanian et al[3] examined the presence of hemoconcentration in relation to ultrasonographic evidence of plasma leakage, but did not evaluate GBWT. In contrast, our study demonstrated a significant correlation of GBWT as measured by ultrasound with both thrombocytopenia and increased hematocrit, two hallmark features of severe dengue.

Our findings from a pediatric population in the Americas are consistent with other reports of ultrasound measurement of GBWT in both children and adults. Although multiple reports have been published on the use of ultrasound in the management of DF, nearly all come from medical centers in Asian countries,[3–6,8–10,12] where the burden of disease is different from that found in Nicaragua and the Americas. One recent article examined GWBT to confirm DHF in Mexico, but in an adult population.[11] Among the reports that explore the use of ultrasound in pediatric dengue cases in Asia, none differentiated between DHF and DF.[5,8,9] The one study that did examine DF and DHF in children did not specifically evaluate GBWT.[3]

Usually, only a minority of hospitalized dengue patients in Nicaragua (~25%) develop manifestations of DHF/DSS. However, it is of vital importance to identify the cases early because DHF/DSS is a potentially fatal condition. The high negative predictive values we found for detecting DHF/DSS demonstrate that ultrasound can be used reliably in outpatient and inpatient settings in triage to rule out DHF/DSS in patients with suspected dengue and to help determine which patients to monitor closely or hospitalize. In conclusion, ultrasound appears to be useful as a tool for diagnosing pediatric DHF/DSS and as a prognostic indication of which patients are at increased risk for developing severe disease.

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NO DECREASE IN CLINDAMYCIN SUSCEPTIBILITY DESPITE INCREASED USE OF CLINDAMYCIN FOR PEDIATRIC COMMUNITY-ASSOCIATED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* SKIN INFECTIONS

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Abstract: A previous study at our institution revealed 98% of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates were susceptible to clindamycin; however, β-lactams were then the predominant empiric treatment. This follow-up chart review study examined subsequent staphylococcal skin and soft tissue infection treatment and susceptibility patterns over a 2-year period. Of 296 *S. aureus* skin and soft tissue infections, 73% were MRSA, of which 87% were community-associated-MRSA; MRSA infections peaked in warm summer months. Despite a significant increase in empiric clindamycin use, 97% of community-associated-MRSA isolates retained susceptibility to clindamycin.

Key Words: MRSA, CA-MRSA, clindamycin, pediatric

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Methicillin-resistant *Staphylococcus aureus* (MRSA) has become a leading cause of community-associated (CA) skin and soft tissue infections (SSTIs) nationwide.[1–3] Clindamycin is an important therapeutic option for treating children with CA-MRSA infections at some institutions; however, there is concern about the increasing threat of clindamycin resistance.[3–6] Ongoing surveillance of local antimicrobial resistance patterns for *S. aureus* is essential for guiding appropriate empiric therapy in patients with suspected staphylococcal infections.

The goals of this 2-year follow-up to a previous surveillance study at our Baltimore institution were to characterize: subsequent trends in the frequency of CA-MRSA among pediatric SSTIs, empiric antibiotic choice for these infections, patterns of antibiotic susceptibility, and risk factors for hospital admission.[3]