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NARRATIVE REVIEW

Review of the role of ultrasound in assessing plasma leakage in dengue fever and a proposed scanning protocol

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Abstract

Background: The clinical course of dengue can range from mild to severe and predicting the course can be challenging. The World Health Organisation (WHO) recommends prognostication via the presence of warning signs, to aid in disposition and management. Plasma leakage is a key warning sign in dengue, and ultrasound can be utilised as a screening tool.
Objectives: The objectives were to describe the literature on the use of ultrasound in dengue, summarise the findings, and propose a standardised point-of-care ultrasound protocol.
Methods: We reviewed the current literature on the role of ultrasound in dengue and its key features.
Results: Ultrasound is a useful tool in the evaluation of patients with dengue and has been shown to be able to detect plasma leakage even prior to clinical and laboratory findings. In particular, gallbladder wall thickening is an early sign that can aid the clinician in prognosticating patients.
Conclusion: Detecting plasma leakage early with ultrasonography can help the clinician determine appropriate disposition and management. We propose a standardised point-of-care ultrasound protocol (FASD) for early detection of plasma leakage in dengue, in the routine care of dengue patients.

KEYWORDS
dengue, emergency medicine, ultrasound

1 | INTRODUCTION

Dengue Fever is a debilitating disease caused by the arbovirus Dengue Virus, endemic in most tropical countries with the largest disease burden in Asia. It is estimated that there are an annual 96 million clinical infections globally[1] and the incidence of infection is rising. In 2023, there was an unprecedented record number of dengue cases worldwide, with over 6.5 million cases and more than 7300 dengue related deaths.[2] It can be difficult to prognosticate dengue patients. Plasma leakage is a significant precursor to severe dengue. Ultrasound is a useful tool to detect plasma leakage early, with positive sonographic signs manifesting even before clinical and laboratory evidence. It is important for clinicians, especially Emergency Physicians (EP), to identify

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these at-risk patients early to guide management and disposition—weighing the risks of clinical deterioration versus the mounting pressure of lack of hospital beds. We propose a point-of-care ultrasound scanning protocol as a risk assessment tool in evaluating the dengue patient.

2 | CLINICAL COURSE OF DENGUE INFECTION

Dengue fever ranges from a mild non-specific febrile illness to a severe form with shock, haemorrhage and multi-organ failure. While most patients recover uneventfully, some develop plasma leakage, which is a significant precursor to severe dengue. Plasma leak is the result of reversible functional derangement of endothelial barrier functions caused by a cytokine storm and the interplay of a host of other mediators.[3–5] The most affected endothelial cells reside in the post-capillary venules[6] and there is a predilection for pleural[7] and peritoneal involvement in dengue. Hypotension can occur if the plasma leak is significant, leading to severe dengue. Plasma leakage is also accompanied by loss of intravascular albumin and coagulation proteins of similar size, which could induce a state of coagulation derangements, leading to major haemorrhagic complications.[8]

With consensus that the clinical course and outcome of dengue infection is often unpredictable, WHO guidelines on dengue infection[9] divides dengue infection into 3 grades of severity; probable dengue, dengue with warning signs and severe dengue. The warning signs (Figure 1) listed in these guidelines serve to guide disposition and risk-stratify those who need more intensive monitoring.

2.1 | Stratification of dengue severity

Studies have shown that the individual warning signs listed by the WHO guidelines have poor sensitivity, with poor positive predictive values in predicting severe disease.[10,11] There are studies showing that certain laboratory markers[3,12] could predict the risk of developing the severe form of dengue. However, these markers are not readily available and the risk stratification of dengue patients remains largely clinical, supported by common laboratory tests.

Plasma leak precedes the development of severe forms of dengue and is associated with increased morbidity and mortality. It is during the critical phase that the patient enters a period of highest risk for developing severe manifestations of plasma leak. Rising haematocrit and fluid accumulation detected clinically are warning signs and proxy indicators of plasma leak. However, there are challenges in utilising these warning signs.

The WHO 2009 criteria do not specify the degree and rate of change in haematocrit and platelet count that is considered significant. In a 5-year multicentre study done in Singapore, the interval from developing warning signs to death was shortest for haematocrit change of $\geq$20% with concurrent platelet count of $<20 \times 10^9$/L.[13] Difficulty also arises during the first encounter with the patient, as the primary care physician or EP may not know the patient's baseline haematocrit. Hence, any change may not be immediately apparent. Changes in haematocrit also need to be interpreted in the appropriate clinical context. For example, a decrease in haematocrit may be caused by severe haemorrhage in one instance, but may also signify that plasma leakage is resolving in another.

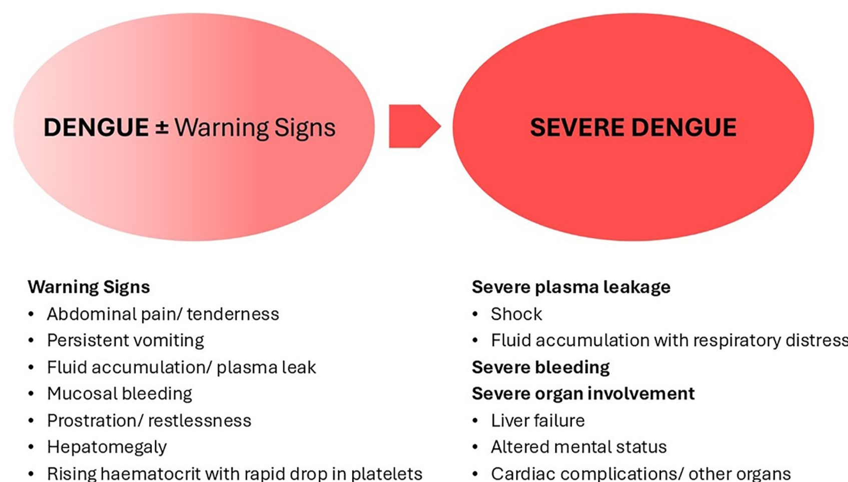


FIGURE 1 Classification of Dengue. Adapted from World Health Organization. (2009). Dengue guidelines for diagnosis, treatment, prevention and control: new edition. World Health Organization.

The clinical detection of plasma leak via physical examination to identify pleural effusion and ascites is difficult since significant amounts of fluid would need to accumulate before reliable detection is possible. Chest radiographs are useful for the detection of pleural effusions but can require as much as 200 mL of fluid before it becomes evident, with sensitivity decreasing in the supine position. In contrast, ultrasound can pick up as little as 20 mL in the pleural cavity.[14] Physical examination allows detection of ascites only in volumes above 500 mL, while ultrasound can demonstrate as little as 100 mL.[15,16]

Patients can appear well despite early signs of shock in the critical phase. Clinical deterioration can be rapid and occur in hours in the critical phase of dengue.[11] Prognosticating dengue patients is a challenge and it is imperative to identify patients with plasma leak early for risk stratification and appropriate disposition.

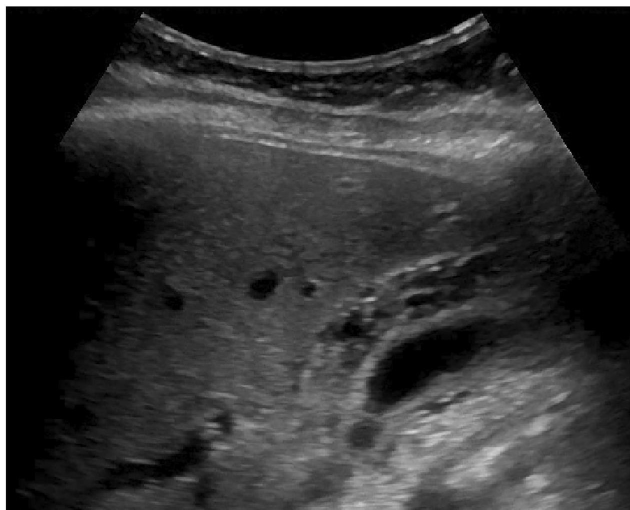


FIGURE 2 Gallbladder wall thickening with honeycomb pattern in dengue.

3 | ROLE OF ULTRASOUND IN DETECTING PLASMA LEAKAGE IN DENGUE FEVER

Point-of-care ultrasonography is an essential aspect of patient care and integral to the practice of Emergency Medicine.[17] It is a timely and portable modality that can be a useful monitoring tool in the evaluation of patients with dengue.[18]

Pleural effusion, ascites and gallbladder wall thickening are common during the critical phase and more importantly, correlate with disease severity.[19–21] Plasma leakage can also be detected using ultrasonography as early as day 3 of fever and point-of-care ultrasonography can detect plasma leakage in some cases before haemoconcentration criteria is met.[22,23]

A study by Balasubramanian et al. compared the utility of signs of plasma leakage—clinical, haemoconcentration, hypoproteinemia, ultrasonography and chest radiography. They concluded that ultrasonography, with a high sensitivity of 91.4% and a negative predictive value of 84.2%, is superior to clinical and laboratory parameters for diagnosing plasma leakage.[24]

3.1 | Gallbladder wall thickening (GBWT)

GBWT more than 3 mm by ultrasound is an early manifestation of plasma leakage and is seen more frequently in severe dengue compared to milder cases (Figure 2).

Nainggolan et al.[23] conducted serial sonographic examinations on dengue patients and showed that GBWT occurred as early as on day 3 of fever even when physical and laboratory examination had not been able to detect plasma leakage, with a positive likelihood ratio of 2.14 (95% CI 1.12—4.12).

GBWT often preceded the detection of ascites or pleural effusion by 1–3 days,[22] with clinical improvement coinciding with resolution of GBWT.[25] This suggests that it can be used as a helpful early predictor of outcome and can be used to predict the recovery or deterioration in dengue.

Setiawan et al. reported GBWT in 32% of mild cases compared to 95% of severe cases.[20] Michels et al.[22] found GBWT in 67% of mild cases compared to 100% of severe cases. Detection of GBWT had a PPV of 21% and a NPV of 91% for severe dengue.

There are 4 distinct GBWT patterns observed in dengue fever: a striated pattern of multiple hypoechoic layers separated by echogenic zones; asymmetric pattern with echogenic tissue projecting into the gallbladder lumen; a central hypoechogenic zone separated by two echogenic layers; and a uniform echogenic pattern.[26]

Early detection of signs of plasma leak such as GBWT can help to risk stratify patients and accord them the appropriate level of monitoring.

3.2 | Pleural and peritoneal free fluid

Ultrasound can detect pleural effusions and ascites earlier than what physical examination alone can achieve.[14–16]

Positive ultrasound findings of pleural effusions and ascites become more frequent as the disease progresses (Figure 3). Venkata sai et al. found that with serial sonographic assessment of dengue patients on day 5–7 of the illness, there was new emergence of ascites (53.1%) and pleural effusions (21.8%).[27]

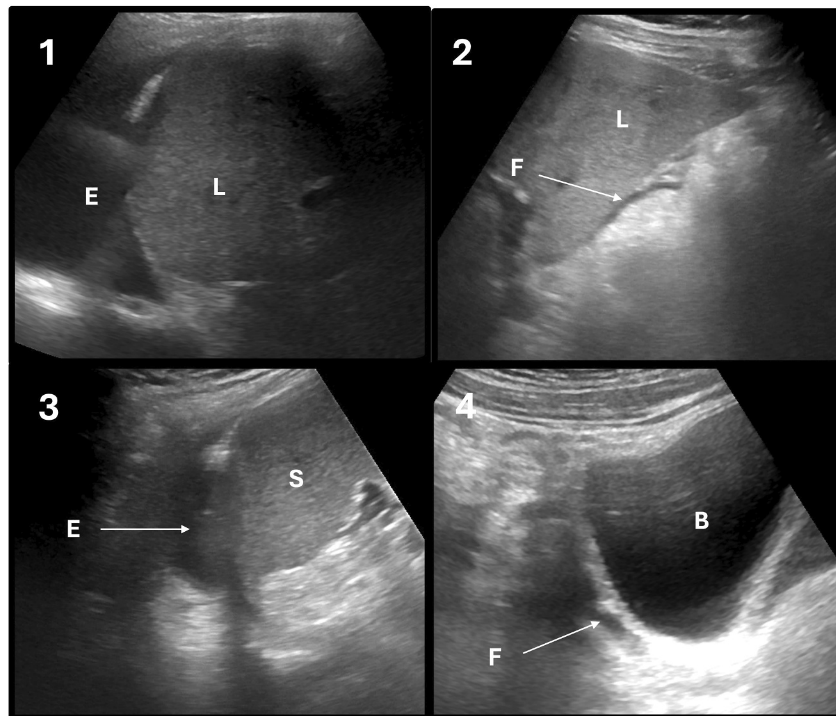


FIGURE 3 1. Right lateral chest at posterior axillary line, E: Pleural effusion, L: Liver. 2. Right flank, F: Free fluid in subhepatic space, L: Liver. 3. Left flank E: Pleural effusion, S: spleen. 4. Pelvic, F: Free fluid in rectovesical pouch, B: Bladder.

The presence of ascites and pleural effusion are predictive indicators of shock,[28] showing a correlation between the presence of pleural effusion and ascites and severity of illness. The magnitude of plasma leakage also positively correlates with the disease severity.[29]

3.3 | Pericardial effusion

With the pathophysiologic predilection for pleural and peritoneal endothelial cells, plasma leakage in other body cavities is rare except in late stages of severe dengue.

In a study on plasma leakage in experimentally induced dengue infection in healthy volunteers, 3 out of 12 subjects developed clinically insignificant pericardial effusion. All three had other concomitant signs of plasma leak, including perihepatic, perisplenic fluid collections and GBWT.[30] Setiawan et al. found small mild pericardial effusion in only 6/75 (8%) patients with severe dengue but in none of the patients with mild illness.[20] Hemodynamically significant pericardial effusions are rare and are reported anecdotally in severe cases of dengue infection.[31,32]

3.4 | Lung parenchymal involvement and pulmonary oedema

Pulmonary oedema is not a standard presentation of plasma leak in dengue. It is usually seen in critically ill cases of severe dengue who develop ARDS or as a complication of fluid therapy.

Lower respiratory tract involvement in dengue is uncommon. In a large series evaluation of 2020 dengue cases, Rodrigues et al.[33] noted chest Computed Tomography studies were performed on 29 patients who had signs and symptoms of respiratory disease. Abnormal findings were seen in 17/29 (58.62%), of which 16 had pleural effusion. Lung parenchymal involvement was seen in 11 patients; the most common pattern being ground glass opacity, followed by consolidation, air space nodules and interlobular septal thickening.

Ultrasound features of pulmonary oedema; namely multiple B-lines and signs of interstitial syndrome are therefore not often seen in dengue fever.[34]

4 | PROPOSED PROTOCOL FOR SCREENING OF DENGUE PATIENTS - FOCUSED ASSESSMENT WITH SONOGRAPHY IN DENGUE (FASD)

Various literature has demonstrated the benefits of use of ultrasound in dengue evaluation and the 2009 WHO guidelines had also suggested its usefulness in diagnosis of plasma leakage. A meta-analysis done was equivocal in its conclusion on whether ultrasound can differentiate severe forms of dengue infection from milder forms.[35] However, the authors noted the limited number of quality papers that could be used in the

meta-analysis and insufficient reporting on the temporality of ultrasonography with regard to the diagnosis.

In clinical practice, ultrasound for the risk stratification of dengue infection is not established as routine practice and to our knowledge, there is no published standardised approach to ultrasound scans in dengue. We believe that the key reasons for this are:

1. Lack of ultrasound access and familiarity for the point-of-care practitioner in the past
2. Clinical practice is guided by the traditional recommendations of platelet and haematocrit monitoring
3. Most ultrasound papers are radiologist-based articles and may not come in the light of point-of-care (POC) conversations
4. There is no published protocol that guides a user on what to focus on in dengue screening[34]

With the progression of Emergency Medicine and point-of-care ultrasonography being a mandated competency in training programs for Emergency Medicine, there is increasing familiarity with this core skill.[17] In the light of current evidence that plasma leak can be associated with increased morbidity and mortality and that clinical deterioration can be rapid in the critical phase of dengue, detection of this phenomenon is crucial in the management of dengue infection. Understanding that there are peculiar patterns of plasma leak in dengue, a systematic approach can be derived.

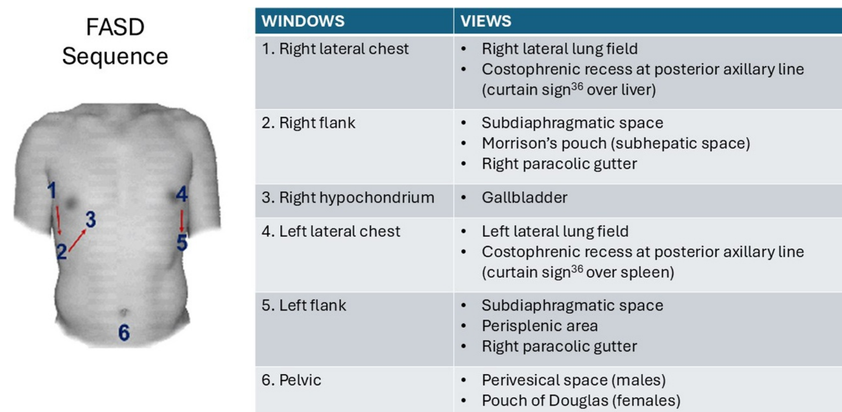
We recommend the Focused Assessment with Sonography in Dengue (FASD) protocol—a systematic approach to the point-of-care ultrasound screening for dengue patients for risk stratification. Most primary care providers are aware of the Extended Focused Assessment with Sonography in Trauma (EFAST) protocol for detection of bleeding in trauma. Given its familiarity, we have adapted the FASD protocol from the EFAST protocol, with similar techniques and scanning windows. This helps to ease the point-of-care practitioner into the adoption of this new protocol.

In FASD, there are 6 windows for scanning (Figure 4) similar to EFAST, with one exception: the replacement of the subxiphoid pericardial scan with a gallbladder scan (right hypochondrium window).

These regions are selected because of following reasons:

1. Plasma leak in dengue affects primarily the pleural and peritoneal cavities.
2. A suprapubic scan is mandatory as small amounts of fluid may only be seen in this location, especially in ambulatory patients.
3. Gallbladder scanning should be done as GBWT is a manifestation that can occur early in the disease prior to onset of significant plasma leak.
4. Pericardial scanning is not routine because pericardial effusion is rarely seen in dengue patients and/or do not cause haemodynamic instability except when they have reached a moribund stage of severe infection.[20,31,32]
5. Pulmonary scanning for oedema is not included as pulmonary oedema in dengue is not a routine feature.[34]

The proposed protocol (FASD) aims to provide a systematic approach for detection of signs of plasma leakage in patients with dengue fever, based on a protocol (EFAST) that most EPs are familiar with. The aim is to detect patients at risk of developing morbidity and hence requiring closer monitoring and fluid resuscitation. The timing of the point-of-care sonography performed with regard to the diagnosis should also be duly recorded for clarity and tracking. A protocol ensures a complete standardised examination to avoid missing crucial findings. It also encourages adequate documentation which can provide accurate data and guide future studies. Utilising this protocol provides valuable and timely information for EPs. This is particularly important as there is usually only a single encounter between a patient and a provider and decisions need to be made with limited information under



WINDOWS	VIEWS
1. Right lateral chest	• Right lateral lung field • Costophrenic recess at posterior axillary line (curtain sign[36] over liver)
2. Right flank	• Subdiaphragmatic space • Morrison's pouch (subhepatic space) • Right paracolic gutter
3. Right hypochondrium	• Gallbladder
4. Left lateral chest	• Left lateral lung field • Costophrenic recess at posterior axillary line (curtain sign[36] over spleen)
5. Left flank	• Subdiaphragmatic space • Perisplenic area • Right paracolic gutter
6. Pelvic	• Perivesical space (males) • Pouch of Douglas (females)

FIGURE 4 FASD sequence.[36]

significant time pressure. Identifying patients at risk of deterioration will aid the practitioner in the judicious allocation of limited resources.

4.1 | Technique and potential pitfalls in scanning

The yield and sensitivity in detecting free fluid using sonography is affected by the patient's position.[37] It is important to include suprapubic views when scanning for free fluid in the peritoneum. In the study by Michels et al., handheld ultrasonography which screened for ascites in the hepatorenal and splenorenal areas but omitted suprapubic views failed to detect plasma leakage seen by conventional ultrasonography in 3/55 patients (5%). They attributed this partly to the fact that conventional ultrasonography had also screened for ascites in the pelvis using suprapubic views.[22] From our experience, this can be a common problem as dengue patients are typically ambulatory patients who wait for consultation seated. If suprapubic views are omitted, the point-of-care practitioner may miss out on positive findings as there may not be sufficient time for fluid to gravitate to the upper quadrants when they lie supine for scans. Moreover, smaller amounts of fluid may not reach the upper quadrants, resulting in a false negative scan.

A small pleural effusion may also be missed if the point-of-care practitioner fails to scan the most dependent part of the lung adjacent to the diaphragm (lung-liver or lung-spleen junction). Hence it is important to be thorough and scan through the area in question to detect smaller amounts of fluid.

We must also bear in mind that GBWT can be present in other infections such as acute cholecystitis and clinical correlation must be made to avoid misdiagnosis and unnecessary interventions. Pseudo-thickening can also be seen in the postprandial state.[38]

5 | CONCLUSION

Plasma leakage is a warning sign in dengue and ultrasound has been shown to be able to detect plasma leakage even prior to clinical and laboratory findings. Detecting plasma leakage early with point-of-care ultrasonography can help the clinician determine appropriate disposition and management. We propose a standardised point-of-care ultrasound protocol (FASD) for early detection of plasma leakage in dengue, in the routine care of dengue patients.

AUTHOR CONTRIBUTIONS

Swee Min Kathleen Khoo: Data curation; resources; writing—original draft; writing—review and editing. **Chun Yue Francis Lee**: Conceptualization; data curation; resources; supervision; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ETHICS STATEMENT

It is not applicable for this article.

INFORMED CONSENT

Written informed consent was obtained for the anonymized ultrasound images to be published in this article.

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PEER REVIEW

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