

Review Article

Dengue Infections and the Surgical Patient

Umesh Jayarajah,^{1*}† Malintha Lahiru,^{2†} Ishan De Zoysa,¹ and Suranjith L. Seneviratne¹

¹Department of Surgery, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka; ²Faculty of Medicine, University of Colombo, Colombo, Sri Lanka

Abstract. Dengue infections are increasing globally and account for significant morbidity and mortality. Severe dengue results in microvascular changes and coagulopathy that may make surgical intervention risky and the overall surgical management challenging. We outline the potential surgical manifestations and complications following dengue infections and describe the clinical, pathogenetic, diagnostic, and treatment aspects of dengue and surgical patients. The main surgical presentations were acute cholecystitis, acute pancreatitis, acute appendicitis, splenic rupture, bowel perforation, gastrointestinal bleeding, and hematomas. Dengue may also mimic an acute abdomen without any true surgical complications. A majority were treated nonoperatively. Misdiagnosis and unnecessary surgical intervention resulted in poor outcomes. Better knowledge of the potential surgical complications would help in early diagnosis, treatment, and referral to specialized centers and thus improve outcomes. A high degree of suspicion of dengue fever is necessary when patients in a dengue-epidemic area present with acute abdomen or bleeding manifestations. In endemic areas, early dengue antigen testing and abdominal imaging before surgical intervention may help in the diagnoses. Multidisciplinary team involvement with case-by-case decision-making is needed for optimal care.

INTRODUCTION

The dengue virus is a single-stranded non-segmented RNA virus, belonging to family Flaviviridae and genus *Flavivirus*. It consists of four serotypes. Dengue infections are increasing globally and account for significant morbidity and mortality.¹ Dengue is endemic in tropical and subtropical regions^{2,3} and causes regular epidemics in countries within the tropical belt.^{4,5} Dengue infections cause a wide spectrum of clinical manifestations, from an asymptomatic state to severe dengue with organ dysfunction and death.^{1,6} Classical dengue fever is characterized by an acute onset of fever associated with headache, retro-orbital pain, severe arthralgia, and myalgia. The more severe forms are dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).⁷ There has been a change in disease patterns with increasing involvement of gastrointestinal, hepatic, renal, hematological, neurological, respiratory, and cardiac systems.^{8–15} Abdominal pain is a recognized feature during the critical phase of DHF.^{1,7} Some patients with dengue may present with surgical complications such as gastrointestinal bleeding, acute pancreatitis, and splenic rupture, and others may mimic an acute abdomen without any true complications.^{16,17}

Severe dengue results in microvascular changes and coagulopathy, which may make surgical intervention risky and the overall surgical management challenging. Better knowledge of the potential surgical complications would help in early diagnosis, treatment, and referral to specialized centers and thus improve outcomes. Early identification of dengue in some patients presenting as acute abdominal emergencies to a surgical unit would help prevent unnecessary surgical interventions. We have critically analyzed the reported surgical complications following dengue and described the clinical,

pathogenetic, diagnostic, and treatment aspects of dengue and surgical patients.

MATERIALS AND METHODS

An extensive search of the published literature before March 31, 2020 was carried out using PubMed, Embase, Scopus, and Google Scholar databases (Supplemental Figure S1). We used the keywords “dengue” OR “dengue viral infections” OR “dengue infections” AND “surgical complications” OR “acute abdomen,” OR “appendicitis,” OR “pancreatitis,” OR “cholecystitis,” OR “splenic rupture” OR “gastrointestinal bleeding” OR “peritonitis” OR “gastrointestinal perforation” OR “peptic ulcer” OR “abdominal wall hematoma.” Only articles published in English language were considered. Initial screening for eligibility (based on titles, abstracts, and keywords of citations from electronic databases) was performed by two investigators. The full-text articles of all relevant records were then evaluated. In doubtful situations, the opinions of senior investigators were sought. All data relating to the clinical presentation, investigation, treatment, and outcomes of dengue in the surgical patient were extracted, categorized, tabulated, and presented descriptively. The studies describing all types of acute surgical presentations were pooled and described qualitatively. Case reports of surgical manifestations in dengue were described separately.

RESULTS

Common causes of acute abdomen in dengue infections.

Abdominal pain is a known clinical manifestation of DHF. An acute abdomen is less common and may mislead the clinician assessing the patient. In general, the studies described acute abdomen as rapid onset abdominal pain and fever as the main complaint with evidence of peritonism on examination.¹⁷ Table 1 shows the case series and case reports of patients with acute abdomen and dengue.^{16–38} A total of 22 studies were found; most were from South Asia (India [$n = 13$], Sri Lanka [$n = 3$], and Pakistan [$n = 3$]) and a few were from Taiwan ($n = 3$). A

* Address correspondence to Umesh Jayarajah or Suranjith L. Seneviratne, Department of Surgery, Faculty of Medicine, University of Colombo, P.O. Box 271, Colombo 8, Sri Lanka 00800. E-mails: umeshe.jaya@gmail.com or suran200@yahoo.co.uk
† These authors contributed equally to this work.

TABLE 1
Common causes of acute abdomen in dengue infections

Article number	Author country	Study type/study period	n/N	Age (years)	Male	Surgical presentations	Surgical interventions	Prolonged hospital stay	Deaths
1	Wu ¹⁸ Taiwan	Retrospective/10 months	10/131	Mean: 48; SD: 15	4	Acute cholecystitis: 10	Cholecystectomy: 2, percutaneous drainage: 1	3	NA
2	Khanna ³³ India	Retrospective/4 months	20	Mean: 35.5; range: 20-67	15	Acalculous cholecystitis: 2, acute appendicitis: 1, acute pancreatitis: 5	Appendicectomy: 1	NA	NA
3	Khor ¹⁹ Taiwan	Retrospective/7 months	14/328	Mean: 44; range: 15-68	4	Acute cholecystitis: 10, nonspecific peritonitis: 3, acute appendicitis: 1	Cholecystectomy: 1, appendicectomy: 1, percutaneous drainage: 1	3	NA
4	Sharma ²⁹ India	Prospective/12 months	14/27	Mean: 29.8; SD: 9.7	21	Acalculous cholecystitis: 14	None	14	1
5	Lee ³⁴ Taiwan	Retrospective/NA	71/774	Mean: 53; range: 18-76	28	Acute pancreatitis: 3	None	0	1
6	Premaratna ²⁰ Sri Lanka	Retrospective/9 months	12/NA	Mean: 28; SD: 4.6	5	Acute appendicitis: 12	Appendicectomy: 1	1	NA
7	Bhatty ³⁸ Pakistan	Retrospective/2 months	11/40	NA	8	Acute acalculous cholecystitis: 8	None	NA	0
8	Weerakoon ³⁶ Sri Lanka	Retrospective/4 months	14/337	Mean: 28; range: 12-47	7	Acute cholecystitis: 5	None	NA	NA
9	Jhamb ²⁶ India	Retrospective/4 months	39/76	Mean: 28; SD: 9.6	NA	Acalculous cholecystitis: 15	None	NA	0
10	Shamim ²¹ Pakistan	Prospective/42 months	43/357	Mean: 29.47; range: 15-72	15	Acute cholecystitis: 26, acute appendicitis: 7, nonspecific peritonitis: 7, acute pancreatitis: 3	Appendicectomy: 5, open cholecystectomy: 3	17	2
11	Chakravarti ³⁷ India	Retrospective/13 months	6/64	NA	NA	Acute cholecystitis: 6	None	NA	0
12	Majumdar ³⁵ India	Prospective/6 months	300	Range: 15-40	NA	Pancreatitis: 45, acalculous cholecystitis: 75	NA	NA	9
13	Ahmad ¹⁶ Pakistan	Retrospective/33 months	121/875	Mean: 34.79; range: 18-70; SD: 12.21	NA	Acute cholecystitis: 46, acute pancreatitis: 19, acute appendicitis: 4, splenic rupture: 1	Splenectomy: 1	NA	2
14	Chatterjee ²⁵ India	Retrospective/6 months	5/180	Mean: 46.7; range: 13-70	NA	Acute pancreatitis: 4, splenic rupture: 1	None	NA	7
15	Desai ³¹ India	Three case reports/NA	3/NA	NA	NA	Appendicular perforation: 3	Exploratory laparotomy: 2, appendicectomy: 1	NA	0
16	Sreeramulu ²⁴ India	Retrospective/35 months	68/955	NA	NA	Acute acalculous cholecystitis: 68	None	NA	0
17	Pothapregada ²⁸ India	Retrospective/29 months	5/254	Mean: 6.9; SD: 3.3	NA	Acalculous cholecystitis: 2, acute pancreatitis: 1, acute appendicitis: 2	None	NA	6
18	Jayasundara ¹⁷ Sri Lanka	Retrospective/12 months	17/3,309	Range: 10-71	7	Acute appendicitis: 8, acute cholecystitis: 5, nonspecific peritonitis: 3, acute pancreatitis: 1	Appendicectomy: 1	1	1
19	Lau ²⁷ India	Retrospective/3 months	65/115	Mean: 31.36; SD: 13.17	NA	Acalculous cholecystitis: 26	None	NA	0
20	Shashirekha ²² India	Retrospective/12 months	183/214	NA	NA	Acalculous cholecystitis: 122, pancreatitis: 24, appendicitis: 4, nonspecific: 33	None	NA	0
21	Chandey ³⁰ India	Prospective/5 months	309/540	Range: 16-65	NA	Acalculous cholecystitis: 210, pancreatitis: 9	None	NA	0
22	Gupta ³² India	Prospective/14 months	165/501	16-72	111	Acalculous cholecystitis: 31, acute pancreatitis: 2, acute appendicitis: 1	None	NA	1

n = dengue cases with acute abdomen; N = total number of DF/DHF cases; NA = not available.

total of 9,365 dengue patients were studied and 1,501 (16%) presented with an acute abdomen. The patients' age ranged from 10 to 76 years. The main causes were acute cholecystitis (45.4%, $n = 681$), acute pancreatitis (7.7% $n = 116$), acute appendicitis (2.7% $n = 40$), appendicular perforation (0.2% $n = 3$), splenic rupture (0.1% $n = 2$), and nonspecific peritonitis (3.1% $n = 46$). Twenty surgical procedures were carried out in these patients (appendectomy [$n = 10$], cholecystectomy [$n = 6$], laparotomy [$n = 3$], and splenectomy [$n = 1$]). The rest were managed conservatively using intravenous fluids, analgesics, and antibiotics. Most patients recovered, 30 died, and a prolonged hospital stay was reported in 39 patients.

Most of the studies described a minority of dengue patients having an acute abdomen, although a few described a higher prevalence. Shashirekha et al.²² reported an acute abdomen in 85.5% of 214 dengue patients; a majority ($n = 122$) developed acute acalculous cholecystitis. In the study by Jayasundara et al.,¹⁷ of 3,309 dengue patients, 17 developed acute abdominal symptoms (acute appendicitis [$n = 8$], acute cholecystitis [$n = 5$], acute pancreatitis [$n = 1$], and nonspecific peritonitis [$n = 3$]). Some studies described acute cholecystitis as the only surgical complication observed in dengue patients. Seeramulu et al.²⁴ reported 68 patients presenting with acute abdomen among 955 DHF patients from India over a 35-month period; all had acute cholecystitis and were managed conservatively. Four studies from India (Jhamb et al.,²⁶ Laul et al.,²⁷ Sharma et al.,²⁹ and Chakravarti et al.³⁷) and one from Pakistan (Bhatti et al.³⁸) describe a total number of 121 dengue patients presenting with acute abdomen. All had acute acalculous cholecystitis and were managed conservatively.

Acute appendicitis associated with dengue infections.

Supplemental Table S1 outlines the reports of acute appendicitis in dengue.^{39–46} Six of the eight patients were male. Common clinical presentations include fever, abdominal pain mainly in the right lower quadrant, and tenderness. Blood pressure, pulse rate, and respiratory rate were normal in all patients. On imaging, two had ultrasonic evidence suggesting appendicitis and in the others, the appendix was not visualized. Three were managed conservatively, and one had a planned interval appendectomy. One underwent reexploration 36 hours after appendectomy because of increasing peritonism, but no bowel pathology was found. A ruptured appendicular mass was noted in another. Of the five where histology was available, two had a normal appendix and three had acute appendicitis with transmural neutrophil infiltration. All patients recovered, and the hospital stay ranged from 6 to 13 days.

Acute cholecystitis associated with dengue infections.

Supplemental Table S2 outlines the reports of acute cholecystitis in dengue.^{47–60} The age of the patients was between 18 and 59 years, and 80% were female. Fever and right upper quadrant abdominal pain were seen in all, one patient was in shock, and the others were hemodynamically stable. Five had a positive Murphy's sign, thrombocytopenia was seen in all, and alkaline phosphatase levels were high. One patient had an abnormal coagulation profile. Imaging (ultrasonography, computed tomography, or magnetic resonance imaging) showed acute acalculous cholecystitis in all. Of the 15 patients, four underwent cholecystectomy and the others were managed conservatively. One of the operated patients died after surgery following severe bleeding, and another had a perforated gall bladder at fundus/body junction. Histology showed changes of

acute cholecystitis. Two of the patients were pregnant at the time of diagnosis and later went on to have successful vaginal deliveries.

Pancreatitis associated with dengue infections. Supplemental Table S3 outlines the reports of acute pancreatitis in dengue.^{61–78} Most of them were from Sri Lanka and India, age range was 10–66 years, and 12 of the 18 were male. Most had fever for > 3 days and epigastric pain, one had melena, and two had hematemesis at the time of admission. On examination, most had low blood pressure, a rapid pulse and respiratory rate, and tender epigastrium. All had low platelet counts and a raised serum amylase or lipase level or both. Liver enzymes were abnormal in most. Imaging (computed tomography, ultrasonography, or magnetic resonance imaging (MRI) scan of the abdomen) showed evidence of acute pancreatitis such as pancreatic edema and acute fluid collection in the majority. Some studies have failed to exclude/mention about other commonest causes of acute pancreatitis such as alcohol and gall stones. Nine developed complications such as bilateral massive pleural effusion, acute lung injury, gastrointestinal bleeding, and liver failure with cerebral edema. Two developed acute kidney injury, shock, and multi-organ dysfunction syndrome, and one patient died. All were managed conservatively. One needed a chest drain, and other interventions included mechanical ventilation, anti-liver failure regime, and blood product transfusion according to their need. Hospital stay ranged from 8 to 21 days.

Splenic rupture associated with dengue infections.

Supplemental Table S4 outlines the reports of splenic rupture in dengue.^{79–94} A majority were from Asia, age ranged from 20 to 52 years, and 15 of 19 were male. All presented with fever for five or more days and abdominal pain, and a majority had signs of shock. Thrombocytopenia, low hemoglobin levels, and low packed cell volume were common. Liver enzymes were abnormal in five patients, and one had an abnormal clotting profile. Imaging showed a splenic hematoma or rupture. There were four deaths: three after a laparotomy and splenectomy and the other before surgical intervention (24 hours after admission). Of the other 15 patients, five were managed conservatively and ten had a laparotomy and splenectomy. There was normal splenic architecture with a capsular tear and no evidence of granuloma or malignancy. Hospital stay ranged from 7 to 30 days.

Other surgical manifestations in patients with dengue fever.

Supplemental Table S5 summarizes the other less common surgical manifestations in dengue.^{16,23,95–114} Seven studies and several case reports/series were found mainly from Asian countries. A total of 296 patients were described. Upper gastrointestinal bleeding was reported in 245 patients (82.7%), and rectal bleeding was reported in 11 patients (3.7%). A total of 147 patients had upper gastrointestinal endoscopic findings of peptic ulcer, hemorrhagic/erosive gastritis, and duodenal and esophageal ulceration. Two patients needed a laparotomy, and 25 patients were managed with endoscopic injections. Two patients with rectal bleeding needed ligation of actively bleeding hemorrhoids. Apart from surgical interventions, a majority needed blood product transfusions, intravenous crystalloids, and intravenous proton pump inhibitors, and a few needed inotropic support and intravenous antibiotics.

Seven (2.4%) patients had a hollow viscous perforation. A previous history of peptic ulcer diseases was not mentioned in

these cases. Three patients had a gastric perforation, and one had ileal and two patients had jejunal perforations. Almost all of them had air fluid levels and gas under diaphragm on abdominal X-rays. All needed emergency laparotomies for repair of the perforation.

Abdominal wall hematomas, predominantly in the rectus sheath, were reported in eight patients. These were managed with percutaneous drainage ($n = 1$), ultrasound-guided aspiration ($n = 1$), and surgical repair of inferior epigastric artery leak ($n = 1$). The rest were managed conservatively. Three cases of retroperitoneal hematomas were reported, and one was managed with endovascular embolization under general anesthesia. Two psoas muscle hematomas were also reported, which were managed conservatively. Fourteen patients developed abscesses which were drained via an incision. Abdominal compartment syndrome was reported in two patients. Surgical wound bleeding was reported in two patients with thrombocytopenia, and one of the patients died.

DISCUSSION

Abdominal symptoms are not uncommon in dengue.¹¹⁵ A large multicenter prospective study found nausea, vomiting, diarrhea, and abdominal pain in 35%, 20%, 16%, and 15% of dengue patients, respectively.¹¹⁵ Right hypochondrial and epigastric tenderness were noted in 26% and 12% patients, respectively. Most of these abdominal symptoms were associated with severe forms of the disease.¹¹⁵ An acute abdomen in dengue has been well-described. Most are single-center reports and involve a small percentage of the total cohort of dengue patients. Most are managed nonoperatively but may have a prolonged hospital stay with complications. Diagnosis of an acute abdomen can be difficult in a critically ill dengue patient. Worsening biochemical parameters, features of edema or inflammation on imaging, clinical deterioration with abdominal guarding, and rigidity would point to the diagnosis. However, similar imaging features may occur secondary to fluid leakage. With borderline presentations, repeated assessments by a multidisciplinary team of specialists would help decide if the patient requires any invasive procedures. The risks of any invasive procedure such as bleeding, secondary infections, surgical stress, and exposure to anesthesia should be weighed against the benefits of removing the source of sepsis or stopping further bleeding. The patients' general health, their clinical condition, and comorbidities would impact on deciding whether invasive procedures should be considered.

Dengue infections may associate with true or apparent surgical acute abdomen because of several reasons. A true acute abdomen may occur as a complication of dengue fever (e.g., ruptured splenic hematomas, upper and lower gastrointestinal bleeding, and abdominal wall hematomas due to coagulopathy associated with dengue). Dengue infections may occur with simultaneous surgical disease (i.e., dual pathology). Such dual pathologies may occur either pathophysiologically unrelated to dengue (e.g., dengue patient with a perforation of a hollow viscus) or pathophysiologically related to it (e.g., or acute acalculous cholecystitis related to dengue). Furthermore, dengue fever may mimic a surgical acute abdomen and may present to surgical specialties. Moreover, surgical complications may be iatrogenic (e.g., abdominal compartment syndrome due to overzealous fluid resuscitation or gastric

perforation related to nonsteroidal anti-inflammatory drug [NSAID] use). Some complications may occur because of complications of dengue and also iatrogenically (e.g., abdominal compartment syndrome due to rectus sheath hematoma¹¹⁶ or due to excessive fluid resuscitation¹¹⁷).

A substantial number of cases of acute abdomen seen in dengue are not because of true complications of dengue or dual pathology but because of clinicians getting deceived by the presentation of dengue to misdiagnose as an acute abdomen.^{17-19,21} Therefore, it is important for clinicians (both physicians and surgeons) to be vigilant, specially in tropics, not only to avoid getting deceived by abdominal symptoms of dengue but also not to miss true acute surgical concerns associated with dengue.

The pathophysiological mechanisms for acute abdomen in dengue are poorly understood.¹⁸ It may be because of direct viral invasion of the abdominal organs such as the appendix, gallbladder wall, pancreas, or spleen leading to inflammation and edema.²¹ A systemic inflammatory response may be another reason. As the vast majority of patients who presented with an acute abdomen had features of DHF or DSS, the systemic inflammatory response and plasma leakage may have led to the edematous and inflammatory changes within organs.^{18,21} An edematous appendix with luminal obstruction may precipitate a secondary bacterial infection and cause appendicitis. The pathogenesis of acute acalculous cholecystitis may be multifactorial.¹⁸ The systemic inflammatory response, endotoxemia, cholestasis, secondary bacterial translocation, spasms of the ampulla of Vater, microangiopathic changes, and ischemia reperfusion injury may contribute.¹⁸ Edema of splenic parenchyma due to fluid leakage or bleeding with expansion of a hematoma within a non-yielding splenic capsule may cause spontaneous splenic rupture. The systemic inflammatory response with coagulopathy may cause spontaneous bleeding or bleeding with trivial trauma, particularly when there is an underlying pathology such as mucosal ulceration.

Most cases of acute abdomen in DHF patients may be treated nonsurgically using fluids and symptom/supportive care.^{19,21} Fever, body aches and pain, nausea, and vomiting could be treated symptomatically.²¹ Aspirin and other NSAIDs should be strictly avoided. Intravenous fluids should be used and the patient kept nil orally.¹¹⁸ Nasogastric decompression may be needed. Routine prophylactic antibiotics should be avoided but may be needed if the patient requires surgery or an invasive procedure.^{17,118,119} Daily monitoring of packed cell volume, platelet counts, and coagulation tests should be carried out in all patients, and liver and renal function tests and blood gases in selected patients.^{19,21} Occult or overt bleeding may need transfusion of packed red cells, fresh frozen plasma, and/or platelets.^{19,21,119} Appropriate organ support may be needed in critically ill patients (e.g., ventilator support in patients with acute severe pancreatitis and acute respiratory distress syndrome).²¹

Appendectomy and/or intravenous antibiotics is the treatment of choice for uncomplicated acute appendicitis. Surgery is the treatment of choice in the case of complicated appendicitis (due to rupture or peritonitis). In some centers, surgery is performed early for uncomplicated acute appendicitis to minimize local and systemic complications.^{120,121} Surgery for acute appendicitis in the context of dengue fever has negative consequences. Khor et al.¹⁹ and Shamim et al.²¹ noted bleeding

requiring blood transfusions, and a prolonged hospital stay was observed.²⁰ Furthermore, of the five patients for whom histology was available, two had a normal appendix and three had acute appendicitis with transmural neutrophil infiltration. Therefore, it is clear that the histopathology does not correlate with the clinical suspicion indicating how clinicians have been misled. Thus, with acute appendicitis in a dengue patient, nonsurgical management with intravenous antibiotics should be considered. If needed, a planned interval appendectomy may be considered.

Acute acalculous cholecystitis was more frequently noted than the calculous form. Acute calculous cholecystitis is managed conservatively followed by delayed cholecystectomy or by emergency cholecystectomy depending on the clinical findings and associated complications.^{16,17} By contrast, acute acalculous cholecystitis is usually managed conservatively with supportive care and intravenous broad spectrum antibiotics and rarely needs cholecystectomy (in cases of gangrenous perforation). Such complications tend to occur in critically ill, hemodynamically unstable, or immunocompromised patients. They may not be fit for surgery and thus managed with minimally invasive procedures such as percutaneous aspiration and drainage.^{16,17} Failing to diagnose and manage DHF in acute cholecystitis may lead to detrimental outcomes. Schmidt-Chanasit et al.⁴⁹ described a German patient who was initially diagnosed with acute acalculous cholecystitis and had a cholecystectomy. The diagnosis of DHF was missed, and the patient died of massive bleeding due to coagulopathy. Thus, DHF needs to be ruled out in such cases with cholecystitis, especially in dengue-endemic regions or in patients with recent travel history to such areas. As plasma leakage with peri-cholecystic edema is a known manifestation in DHF, there may be diagnostic difficulty in identifying acalculous cholecystitis in DHF by ultrasonography. Gallbladder wall thickening and peri-cholecystic edema may be noted in the leaking phase of dengue, raising a diagnostic dilemma among dengue patients. Therefore, clinicians should be cautious in diagnosing acute cholecystitis in dengue patients.

The main stay of management of acute pancreatitis is supportive care. Only very selected patients need surgery within the first few days of symptoms. Similarly, acute pancreatitis in a patient with DHF would only rarely need surgical intervention. Acute pancreatitis in a dengue patient is associated with prolonged hospital stay and complications such as acute lung injury, massive pleural effusion, gastrointestinal bleeding, and acute kidney injury. Because aggressive fluid resuscitation is needed in acute pancreatitis, DHF patients may be at risk of life-threatening fluid overload, especially in the convalescent phase. Intensive monitoring of fluid management may be needed in an intensive care unit setting.

A majority of the splenic ruptures in dengue presented as an emergency. Most needed surgical intervention (laparotomy and splenectomy). Splenic rupture may cause massive hemorrhage, especially in critically ill dengue patients with coagulopathy. In such patients, diagnosing intra-abdominal bleeding may be difficult by ultrasonography, and contrast enhanced computed tomography (CT) computed tomography (CT) scanning may be needed. At present, the exact etiology of splenic rupture in dengue is unclear. Fluid leakage may make lead to a congested/edematous spleen. Bleeding within the spleen (due to coagulopathy) precipitated by minor trauma

may lead to rapid expansion of the hematoma. A rigid and non-yielding splenic capsule may trigger rupture of the otherwise normal spleen. Surgery is the mainstay of treatment, but minimally invasive procedures such as angioembolization of the splenic artery may be considered in patients not fit for surgery.

Uncomplicated appendicitis and cholecystitis in dengue usually resolve spontaneously. Wu et al.¹⁸ found the gallbladder wall thickening to return to normal following recovery and cholecystectomy was not necessary. However, any complications such as gangrene or perforation would need surgical intervention. Performing surgery in a critically ill patient is challenging and has more complications. Minimally invasive approaches such as image-guided percutaneous drainage may be considered.^{19,21,119} The bleeding tendency due to coagulopathy, both during and after surgery, is challenging to manage. At present, guidance on the perioperative correction of coagulopathy in critically ill dengue patients is limited. Thromboelastography with targeted correction would avoid excessive transfusion of blood products and fluid overload. Studies identifying factors that predict a failure of conservative management in acute abdomen in dengue are lacking. Thus decisions need to be taken on a case-by-case basis by a multidisciplinary team involving a physician, surgeon, critical care specialist, radiologist, and anesthetist. Postoperative complications such as intra-abdominal bleeding, wound hematoma, wound dehiscence, and surgical site infection have been reported in critically ill dengue patients. Thus, correction of coagulopathy should be carried out throughout the perioperative period.

Misinterpretation of acute abdominal signs/symptoms may occur frequently in dengue fever.¹⁷ A prior history of gallstone disease or pancreatitis may confuse clinical decision-making. Furthermore, neutropenia, lymphocytosis, and thrombocytopenia may not be seen in all dengue patients at an early stage of disease. Jayasundara et al.¹⁷ found the hematological changes of dengue fever in only two-thirds of patients at an early stage of the disease (i.e., in the first 24 hours). Misdiagnosing dengue as a surgical acute abdomen may result in significant morbidity and mortality. Surgical intervention during the critical phase of dengue may significantly compromise disease homeostasis. Failure of recognition of the critical phase of dengue may lead to DSS and even death. Also, it is important to note that dengue guidelines may not comply with other surgical disease guidelines. For example, limited fluid management in dengue does not comply with liberal fluid management in pancreatitis, making the management of pancreatitis in a dengue patient challenging. Intramuscular analgesia and NSAIDs which are commonly used analgesics for perceived acute abdomen may worsen coagulopathy and give rise to hematomas and other bleeding manifestations in a dengue patient. Furthermore, thromboembolism prophylaxis in surgical abdomens does not comply with DF management because of the bleeding tendency. A big risk with misdiagnosing dengue fever as an acute abdomen is an invasive surgical procedure, which may lead to severe complications.¹⁷

Recommendations. Dengue fever should be considered as a possible cause in patients from a dengue-endemic area presenting with acute abdomen or bleeding manifestations or patients with a relevant travel history. Such patients should be evaluated with basic hematological tests, early dengue antigen/serology, and imaging.

Aspirin and other NSAIDs should be strictly avoided. Routine prophylactic antibiotics should be avoided, except when surgery is needed or invasive procedures are to be undertaken. Daily monitoring of full blood count, coagulation tests and, liver and renal function tests should be performed. Because surgery is risky and challenging in dengue patients, this should be reserved for highly selected patients with perforation, gangrene, and uncontrollable hemorrhage. Minimally invasive methods such as percutaneous drainage for abscesses and collections and angioembolization for splenic rupture or bleeding should be considered. Uncomplicated cases of acute cholecystitis, appendicitis, and pancreatitis should be managed conservatively. From a surgical point of view, unless there is gangrenous appendicular/gallbladder/viscus perforation, surgery could be avoided in the hyperacute setting. Thromboelastography with targeted correction of coagulopathy would be beneficial to avoid excessive transfusion of blood products and fluid overload. Decisions on care and invasive procedures should be taken on a case-by-case basis by a multidisciplinary team involving a physician, surgeon, critical care specialist, radiologist, and anesthetist.

CONCLUSION

We have outlined the surgical manifestations and complications following dengue infections and described the clinical, pathogenetic, diagnostic, and treatment aspects of dengue and surgical patients. Surgical manifestations are not uncommon, and a majority can be managed nonoperatively or by minimally invasive procedures. Common surgical manifestations include acute acalculous cholecystitis, acute pancreatitis, acute appendicitis, splenic rupture, bowel perforation, gastrointestinal bleeding, and hematomas. A high degree of suspicion of dengue fever is necessary when a patient from a dengue-endemic area presents with acute abdomen or bleeding manifestations. Misdiagnosis and unnecessary surgical procedures lead to poor outcomes. Such misdiagnoses can be prevented by evaluation with basic hematological tests, early dengue antigen tests/serology, and imaging. Multidisciplinary team involvement with case-by-case decision-making is needed for optimal care.

Received August 9, 2020. Accepted for publication October 8, 2020.

Published online November 9, 2020.

Note: Supplemental figure and tables appear at www.ajtmh.org.

Acknowledgments: The American Society of Tropical Medicine and Hygiene (ASTMH) assisted with publication expenses.

Authors' addresses: Umesh Jayarajah, Ishan De Zoysa, and Suranjith L. Seneviratne, Department of Surgery, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka, E-mails: umeshe.jaya@gmail.com, ishandz@hotmail.com, and suran200@yahoo.co.uk. Malintha Lahiru, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka, E-mails: malinthalahiru@gmail.com.

REFERENCES

- World Health Organization, 2009. *Dengue Guidelines for Diagnosis, Treatment, Prevention and Control: New edition*. Available at: <https://apps.who.int/iris/handle/10665/44188>. Accessed August 1, 2020.
- Malavige GN, Fernando S, Fernando DJ, Seneviratne SL, 2004. Dengue viral infections. *Postgrad Med J* 80: 588–601.
- Jayarajah U et al., 2020. Comparing the 2009 and 1997 World Health Organization dengue case classifications in a large cohort of South Asian patients. *J Infect Dev Ctries* 14: 781–787.
- Jayarajah U, Faizer S, de Zoysa I, Seneviratne SL, 2017. A large dengue epidemic affects Sri Lanka in 2017. *Int J Progressive Sci Tech* 6: 84–85.
- de Silva PK, Jayawardena P, Jayarajah U, Faizer S, Perera L, Kannangara V, de Zoysa I, Seneviratne PS, 2017. Improving clinical outcomes through setting up of a specialised dengue treatment unit. *Int J Adv Res* 5: 1152–1153.
- Jayarajah U, Dissanayake U, Edirisinghe K, Seneviratne SL, 2020. The World Health Organization dengue case classifications. *Galle Med J* 25: 74–79.
- Verdeal JCR, Costa Filho R, Vanzillotta C, de Macedo GL, Bozza FA, Toscano L, Prata A, Tanner AC, Machado FR, 2011. Guidelines for the management of patients with severe forms of dengue. *Rev Bras Ter Intensiva* 23: 125–133.
- Seneviratne S, Malavige G, De Silva H, 2006. Pathogenesis of liver involvement during dengue viral infections. *Trans R Soc Trop Med Hyg* 100: 608–614.
- Kabra S, Juneja R, Jain Y, Singhal T, Dar L, Kothari S, Broor S, 1998. Myocardial dysfunction in children with dengue haemorrhagic fever. *Natl Med J India* 11: 59–61.
- Jayarajah U, Seneviratne SL, Gurugama P, Wanigasuriya KP, 2017. Microalbuminuria and dengue viral infections. *Southeast Asian J Trop Med Public Health* 48: 938.
- Gurugama P, Jayarajah U, Wanigasuriya K, Wijewickrema A, Perera J, Seneviratne SL, 2018. Renal manifestations of dengue virus infections. *J Clin Virol* 101: 1–6.
- Dissanayake HA, Seneviratne SL, 2018. Liver involvement in dengue viral infections. *Rev Med Virol* 28: e1971.
- Ng D, Ghosh A, Jit M, Seneviratne SL, 2017. Mini-review: can non-human leucocyte antigen genes determine susceptibility to severe dengue syndromes? *Trans R Soc Trop Med Hyg* 111: 384–392.
- Perera L, De Zoysa N, Jayarajah U, Senanayake N, De Zoysa I, Seneviratne SL, 2020. Transfusion-transmissible dengue infections. *Trans R Soc Trop Med Hyg* 114: traa075.
- Jayarajah U, Basnayake A, Nagodavithane K, Jayasinghe J, Samarasekera DN, 2020. Atypical presentation of severe dengue in a patient following a major abdominal surgery. *Case Reports in Infectious Diseases* 2020: ID 2916107. Available at: <https://doi.org/10.1155/2020/2916107>. Accessed August 1, 2020.
- Ahmad F, Nadeem A, Faisal MS, Shaikat M, Siddique K, 2013. Management experience of surgical complications of dengue fever patients at hameed Latif hospital, Lahore. *Ann King Edward Med Univ* 19: 49.
- Jayasundara B, Perera L, de Silva A, 2016. Dengue fever may mislead the surgeons when it presents as an acute abdomen. *Asian Pac J Trop Med* 10: 15–19.
- Wu KL, Changchien CS, Kuo CM, Chuah SK, Lu SN, Eng HL, Kuo CH, 2003. Dengue fever with acute acalculous cholecystitis. *Am J Trop Med Hyg* 68: 657–660.
- Khor BS, Liu JW, Lee IK, Yang KD, 2006. Dengue hemorrhagic fever patients with acute abdomen: clinical experience of 14 cases. *Am J Trop Med Hyg* 74: 901–904.
- Premaratna R, Bailey M, Ratnasena B, De Silva H, 2007. Dengue fever mimicking acute appendicitis. *Trans R Soc Trop Med Hyg* 101: 683–685.
- Shamim M, 2010. Frequency, pattern and management of acute abdomen in dengue fever in Karachi, Pakistan. *Asian J Surg* 33: 107–113.
- Shashirekha C, Sreeramulu P, Ravikiran H, 2016. Surgical presentations with abdominal pain in dengue fever. *Int Surg J* 3: 754–756.
- Prabhu Singh R, Kumar S, Chandra A, 2017. Dengue fever outbreak in surgical patients: diagnostic challenges and outcome impact, 2014. *Open Access J Surg* 3: 555603.
- Sreeramulu P, Shashirekha C, Katti P, 2014. Incidence and management of acalculus cholecystitis in dengue fever-A retrospective study. *Int J Biomed Adv Res* 5: 422–424.
- Chatterjee N, Mukhopadhyay M, Ghosh S, Mondol M, Das C, Patar K, 2014. An observational study of dengue fever in a

- tertiary care hospital of eastern India. *J Assoc Physicians India* 62: 224–227.
26. Jhamb R, Kumar A, Ranga GS, Rathi N, 2010. Unusual manifestations in dengue outbreak 2009, Delhi, India. *J Commun Dis* 42: 255–261.
 27. Laul A, Laul P, Merugumala V, Pathak R, Miglani U, Saxena P, 2016. Clinical profiles of dengue infection during an outbreak in northern India. *J Trop Med* 2016: 5917934.
 28. Pothapregada S, Kamalakannan B, Thulasingham M, 2016. Clinical profile of atypical manifestations of dengue fever. *Indian J Pediatr* 83: 493–499.
 29. Sharma N, Mahi S, Bhalla A, Singh V, Varma S, Ratho RK, 2006. Dengue fever related acalculous cholecystitis in a North Indian tertiary care hospital. *J Gastroenterol Hepatol* 21: 664–667.
 30. Chandey M, Kaur H, Kaur S, 2017. Acute acalculous cholecystitis in dengue fever patients. *Int J Adv Med* 4: 375–377.
 31. Desai G, Gupta S, Ali S, Aggarwal L, Thomas S, 2014. Appendicular perforation in dengue fever: our experience. *Asian Pac J Trop Dis* 4: S571–S572.
 32. Gupta B, Nehara H, Parmar S, Meena S, Gajraj S, Gupta J, 2017. Acute abdomen presentation in dengue fever during recent outbreak. *J Acute Dis* 6: 198.
 33. Khanna S, Vij JC, Kumar A, Singal D, Tandon R, 2004. Dengue fever is a differential diagnosis in patients with fever and abdominal pain in an endemic area. *Ann Trop Med Parasitol* 98: 757–760.
 34. Lee IK, Khor BS, Kee KM, Yang KD, Liu JW, 2007. Hyperlipasemia/pancreatitis in adults with dengue hemorrhagic fever. *Pancreas* 35: 381–382.
 35. Majumdar R, Jana CK, Ghosh S, Biswas U, 2012. Clinical spectrum of dengue fever in a tertiary care centre with particular reference to atypical presentation in the 2012 outbreak in Kolkata. *J Indian Med Assoc* 110: 904–906.
 36. Weerakoon KGAD, Chandrasekaramb S, Jayabahu JPSNK, Gunasena S, Kularatne SAM, 2009. Acute abdominal pain in dengue haemorrhagic fever: a study in Sri Lanka. *Dengue Bull.* 33: 70–74.
 37. Chakravarti A, Suresh K, Neha, Shweta, Malik S, 2009. Dengue outbreak in Delhi in 2009: study of laboratory and clinical parameters. *J Commun Dis* 44: 163–168.
 38. Bhatti S, Shaikh NA, Fatima M, Sumbhuani AK, 2009. Acute acalculous cholecystitis in dengue fever. *J Pak Med Assoc* 59: 519–521.
 39. Senanayake MP, Samarasinghe M, 2014. Acute appendicitis complicated by mass formation occurring simultaneously with serologically proven dengue fever: a case report. *J Med Case Rep* 8: 116.
 40. Osuna-Ramos JF, Silva-Gracia C, Maya-Vacio GJ, Romero-Utrilla A, Ríos-Burgueño ER, Velarde-Félix JS, 2017. Coexistence of acute appendicitis and dengue fever: a case report. *Cir Cir* 85 (Suppl 1): 44–48.
 41. McFarlane ME, Plummer JM, Leake PA, Powell L, Chand V, Chung S, Tulloch K, 2013. Dengue fever mimicking acute appendicitis: a case report. *Int J Surg Case Rep* 4: 1032–1034.
 42. Low YN, Keong BCM, 2016. Appendicular mass complicating acute appendicitis in a patient with dengue fever. *Med J Malaysia* 71: 83–84.
 43. Kumarasena LPP, Bandara S, Pubudu WPG, Jayasundara B, Silva AD, 2015. A case of dengue fever with acute appendicitis: not dengue fever mimicking appendicitis. *Sri Lanka J Surg* 32: 33–35.
 44. Kumar L, Singh M, Saxena A, Kolhe Y, Karande SK, Singh N, Venkatesh P, Meena R, 2015. Unusual presentation of dengue fever leading to unnecessary appendectomy. *Case Rep Infect Dis* 2015: 465238.
 45. Kang YJ, Choi SY, Kang IJ, Lee JE, Seo MH, Lee TH, Ghim BK, 2009. Dengue fever mimicking acute appendicitis: a case report. *Infect Chemother* 41: 236–239.
 46. Albalawi A, Alharbi M, Hamdi A, Alahmadi M, Almaghrabi B, Albalawi W, AlRubayyi M, Alanazi M, Alanazi G, Alnahawa H, 2018. Dengue fever mimicking acute appendicitis: a case report. *Int J Adv Res* 6: 647–649.
 47. Tan YM, Ong CC, Chung AY, 2005. Dengue shock syndrome presenting as acute cholecystitis. *Dig Dis Sci* 50: 874–875.
 48. Sood A, Midha V, Sood N, Kaushal V, 2000. Acalculous cholecystitis as an atypical presentation of dengue fever. *Am J Gastroenterol* 95: 3316–3317.
 49. Schmidt-Chanasit J, Tenner-Racz K, Poppert D, Emmerich P, Frank C, Dinges C, Penning R, Nerlich A, Racz P, Gunther S, 2012. Fatal dengue hemorrhagic fever imported into Germany. *Infection* 40: 441–443.
 50. Nasim A, 2009. Dengue fever presenting as acute acalculous cholecystitis. *J Coll Physicians Surg Pak* 19: 531–533.
 51. Mia MA MM, Perveen S, Chowdhury N, Ahmed M, Rahman S, 2017. Acute acalculous cholecystitis in dengue hemorrhagic fever-A case report. *JBCPS* 155–157.
 52. Marasinghe JP, Sriyasinghe RY, Wijewantha VI, Gunaratne KA, Wijeyaratne CN, 2011. Acute acalculous cholecystitis due to dengue hemorrhagic fever during pregnancy. *J Obstet Gynaecol Res* 37: 1489–1492.
 53. Kuna A, Wroczynska A, Gajewski M, Felczak-Korzybska I, Nahorski WL, 2016. A case of acalculous cholecystitis in the course of dengue fever in a traveller returned from Brazil. *Int Marit Health* 67: 38–41.
 54. Karunatilake H, Vithiya K, Arasalingam A, Malavan R, Kumara DS, 2008. Acalculous cholecystitis and dengue fever. *Ceylon Med J* 53: 30.
 55. Jaufeerally F, Surrin S, Chang P, 2007. Acute acalculous cholecystitis in dengue hemorrhagic fever. *Indian J Med Sci* 61: 613–614.
 56. Hisamonie Koh F, Misli H, Chong VH, 2011. Acute acalculous cholecystitis secondary to dengue fever. *Brunei Int Med J* 7: 45–49.
 57. Goh BK, Tan SG, 2006. Case of dengue virus infection presenting with acute acalculous cholecystitis. *J Gastroenterol Hepatol* 21: 923–924.
 58. Deshmukh N, Rath A, Reddy MS, M N, 2018. Gallbladder perforation in acute acalculous cholecystitis: an atypical manifestation of dengue fever. *Int Surg J* 5: 1943–1945.
 59. Das T, Kundu A, Maity A, Manna S, 2013. Acute acalculous cholecystitis in dengue fever. *J Assoc Physicians India* 61: 750–752.
 60. Berrington WR, Hitti J, Casper C, 2007. A case report of dengue virus infection and acalculous cholecystitis in a pregnant returning traveler. *Trav Med Infect Dis* 5: 251–253.
 61. Wijekoon CN, Wijekoon PW, 2010. Dengue hemorrhagic fever presenting with acute pancreatitis. *Southeast Asian J Trop Med Public Health* 41: 864–866.
 62. Sudulagunta SR, Sodalagunta MB, Sepehrar M, Bangalore Raja SK, Nataraju AS, Kumbhat M, Sathyanarayana D, Gummadi S, Burra HK, 2016. Dengue shock syndrome. *Oxf Med Case Rep* 2016: omw074.
 63. Simadibrata M, 2012. Acute pancreatitis in dengue hemorrhagic fever. *Acta Medica Indones* 44: 57–61.
 64. Seetharam P, Rodrigues G, 2010. Dengue fever presenting as acute pancreatitis. *Eurasian J Med* 42: 151–152.
 65. Nawal CL, Meena PD, Chejara RS, Jain S, Marker S, Tuteja V, 2018. Dengue fever as a rare cause of acute pancreatitis. *J Assoc Physicians India* 66: 82–83.
 66. Lee CY, Tsai HC, Lee SS, Lin CK, Huang JS, Chen YS, 2013. Dengue hemorrhagic fever presenting with hemorrhagic pancreatitis and an intramural hematoma of the duodenal wall: a case report and review of the literature. *Southeast Asian J Trop Med Public Health* 44: 400–408.
 67. Kumar S, Lakhiwal R, Bhandiwad C, Chhimpaa A, Gupta A, 2017. Dengue fever presenting as acute pancreatitis. *Int J Res Med Sci* 5: 2995.
 68. Kumar KJ, Chandrashekar A, Basavaraja CK, Kumar HC, 2016. Acute pancreatitis complicating dengue hemorrhagic fever. *Rev Soc Bras Med Trop* 49: 656–659.
 69. Kodisinghe SFA, 2011. A case of Dengue fever complicated by acute pancreatitis. *Galle Med J* 16: 43–44.
 70. Karoli R, Fatima J, Singh G, Maini S, 2012. Acute pancreatitis: an unusual complication of dengue fever. *J Assoc Physicians India* 60: 64–65.
 71. Jusuf H, Sudjana P, Djumhana A, Abdurachman SA, 1998. DHF with complication of acute pancreatitis related hyperglycemia: a case report. *Southeast Asian J Trop Med Public Health* 29: 367–369.
 72. Jain V, Gupta O, Rao T, Rao S, 2014. Acute pancreatitis complicating severe dengue. *J Global Infect Dis* 6: 76–78.

73. Gonzalez-Fontal GR, Henao-Martinez AF, 2011. Dengue hemorrhagic fever complicated by pancreatitis. *Braz J Infect Dis* 15: 490–492.
74. Correa R, Ortega-Loubon C, Zapata-Castro LE, Armién B, Culquichicon C, 2019. Dengue with hemorrhagic manifestations and acute pancreatitis: case report and review. *Cureus* 11: e4895.
75. Chen TC, Perng DS, Tsai JJ, Lu PL, Chen TP, 2004. Dengue hemorrhagic fever complicated with acute pancreatitis and seizure. *J Formos Med Assoc* 103: 865–868.
76. Anam AM, Rabbani R, Shumy F, Polash MM, 2016. Subsequent pancreatitis and haemothorax in a patient of expanded dengue syndrome. *Trop Doct* 46: 40–42.
77. Agrawal A, Jain N, Gutch M, Shankar A, 2011. Acute pancreatitis and acute respiratory distress syndrome complicating dengue haemorrhagic fever. *BMJ Case Rep* 2011: bcr1020114891.
78. Krithika AP, Ramya R, 2018. Acute Pancreatitis: a late complication of dengue fever. *Int J Contemp Pediatr* 5: 676–677.
79. Sharma S, Kadhiraavan T, 2008. Spontaneous splenic rupture in dengue hemorrhagic fever. *Am J Trop Med Hyg* 78: 7.
80. Seravali M, Santos A, Costa C, Rangel D, Valentim L, Gonçalves R, 2009. Spontaneous splenic rupture due to dengue fever: report of two cases. *Braz J Infect Dis* 12: 538–540.
81. Redondo MC et al., 1997. Hemorrhagic dengue with spontaneous splenic rupture: case report and review. *Clin Infect Dis* 25: 1262–1263.
82. Rapp C, Debord T, Imbert P, Lambotte O, Roué R, 2002. Splenic rupture in infectious disease: splenectomy or conservative treatment? Report of three cases. *Rev Med Interne* 23: 85–91.
83. Pungjitrapai A, Tantawichien T, 2008. A fatal case of spontaneous rupture of the spleen due to dengue virus infection: case report and review. *Southeast Asian J Trop Med Public Health* 39: 383–386.
84. Naik RP, Joshipura VP, Patel NR, Thakkar RM, 2010. Spontaneous rupture of spleen in dengue virus infection. *Trop Gastroenterol* 31: 237–239.
85. Mukhopadhyay M, Chatterjee N, Maity P, Patar K, 2014. Spontaneous splenic rupture: a rare presentation of dengue fever. *Indian J Crit Care Med* 18: 110–112.
86. Miranda L, Miranda SJC, Rolland M, 2004. Case report: spontaneous rupture of the spleen due to dengue fever. *Braz J Infect Dis* 7: 423–425.
87. Liyanage AS, Kumara MT, Rupasinghe DK, Sutharshan S, Gamage BD, Kulathunga A, de Silva WM, 2011. An unusual cause for shock in dengue fever. *Ceylon Med J* 56: 120–121.
88. Gopie P, Teelucksingh S, Naraynsingh V, 2012. Splenic rupture mimicking dengue shock syndrome. *Trop Gastroenterol* 33: 154–155.
89. de Souza LJ, de Azevedo J, Kohler LIA, Barros LF, Lima MA, Silva EM, Mohana-Borges R, Nunes PCG, Paes MV, 2017. Evidence of dengue virus replication in a non-traumatic spleen rupture case. *Arch Virol* 162: 3535–3539.
90. de Silva WT, Gunasekera M, 2015. Spontaneous splenic rupture during the recovery phase of dengue fever. *BMC Res Notes* 8: 286.
91. de Moura Mendonça LS, de Moura Mendonça ML, Parrode N, Barbosa M, Cardoso RM, de Araújo-Filho JA, 2011. Splenic rupture in dengue hemorrhagic fever: report of a case and review. *Jpn J Infect Dis* 64: 330–332.
92. Couvelard A, Marianneau P, Bedel C, Drouet MT, Vachon F, Hénin D, Deubel V, 1999. Report of a fatal case of dengue infection with hepatitis: demonstration of dengue antigens in hepatocytes and liver apoptosis. *Hum Pathol* 30: 1106–1110.
93. Bhaskar E, Moorthy S, 2012. Spontaneous splenic rupture in dengue fever with non-fatal outcome in an adult. *J Infect Dev Ctries* 6: 369–372.
94. Anam AM, Polash M, Islam M, Bhuiyan M, Nooruzzaman ARM, Uddin M, 2013. Spontaneous splenic rupture in severe dengue. *Bangladesh Crit Care J* 1: 59–62.
95. Chiu YC et al., 2005. Endoscopic findings and management of dengue patients with upper gastrointestinal bleeding. *Am J Trop Med Hyg* 73: 441–444.
96. Tsai CJ, Kuo CH, Chen PC, Changcheng CS, 1991. Upper gastrointestinal bleeding in dengue fever. *Am J Gastroenterol* 86: 33–35.
97. Abdulkareem Z et al., 2017. Gastroendoscopic manifestations in dengue fever patients. *EC Gastroenterol Dig Syst* 1: 233–239.
98. Wang JY, Tseng CC, Lee CS, Cheng KP, 1990. Clinical and upper gastroendoscopic features of patients with dengue virus infection. *J Gastroenterol Hepatol* 5: 664–668.
99. Lim CH, Ng BHS, Kan F, 2017. Upper gastrointestinal haemorrhage in severe dengue: to scope or not to scope? *Med J Malaysia* 72: 55–57.
100. Sari EF, Syam AF, Nainggolan L, 2008. Cause of upper gastrointestinal tract bleeding in dengue hemorrhagic fever patient. *Indonesian J Gastroenterol Hepatol Dig Endosc* 9: 30–34.
101. Elmakki E, 2018. An usual cause of massive upper gastrointestinal bleeding. *Gastroenterology* 154: e3–e4.
102. Kularatne SAM, Ralapanawa U, Dalugama C, Jayasinghe J, Rupasinghe S, Kumarihamy P, 2018. Series of 10 dengue fever cases with unusual presentations and complications in Sri Lanka: a single centre experience in 2016. *BMC Infect Dis* 18: 674.
103. Ng CY, Lee SL, Foo SL, 2017. Perforated gastric ulcer in severe dengue infection: a case report. *Med J Malaysia* 72: 244–245.
104. Pillai M, Rao G, 2019. Peptic perforation in paediatric case of dengue: rare presentation. *Int Surg J* 6: 3418.
105. Mandhane N, Ansari S, Shaikh T, Deolekar S, Mahadik A, Karandikar S, 2017. Dengue presenting as gastric perforation: first case reported till date. *Int J Res Med Sci* 3: 2139–2140.
106. Alam S, Bhuiya M, Islam A, Paul S, 2002. Perforated gas containing hollow viscous: a study in a hospital, Bangladesh. *Orion* 12: 1–7.
107. Kumar P, Gupta A, Pandey A, Kureel SN, 2016. Ileal perforation associated with dengue in the paediatric age group: an uncommon presentation. *BMJ Case Rep* 2016: bcr2016216257.
108. Sharma A, Bhatia S, Singh R, Malik G, 2014. Dengue fever with rectus sheath hematoma: a case report. *J Family Med Prim Care* 3: 159–160.
109. Nelwan EJ, Angelina F, Adiwinata R, Matondang S, Andriono P, 2017. Spontaneous rectus sheath hematomas in dengue hemorrhagic fever: a case report. *IDCases* 10: 35–37.
110. Waseem T, Latif H, Shabbir B, 2014. An unusual cause of acute abdominal pain in dengue fever. *Am J Emerg Med* 32: 819.e3–819.e4.
111. Kaur H, Girgila K, 2016. Rectus sheath haematoma complicating dengue haemorrhagic fever—a case report. *J Int J Res Med Sci* 5. Available at: <https://dx.doi.org/10.18203/2320-6012.ijrms20164578>.
112. Pallivalappil B, Supreeth R, Dipu KP, Manappallil R, 2018. Spontaneous muscle hematoma in dengue hemorrhagic fever: a report of four cases. *J Case Rep* 8: 115–119.
113. Koshy J, John M, Rathore S, George U, 2014. Spontaneous muscle hematomas in a patient with Dengue hemorrhagic fever. *CHRISMED J Health Res* 1: 201–202.
114. Jain AKC, Viswanath S, 2017. Multiple jejunal perforations in dengue. *Int J Adv Med* 1: 153–154.
115. Jayarajah U, de Silva PK, Jayawardana P, Dissanayake U, Kulatunga A, Fernando H, Perera L, Kannangara V, Udayangani C, Peiris R, 2018. Pattern of dengue virus infections in adult patients from Sri Lanka. *Trans R Soc Trop Med Hyg* 112: 144–153.
116. Ghosh S, Singh R, Ghosh S, Chawla A, 2018. Unusual surgical emergency in a patient of dengue haemorrhagic fever: spontaneous rectus sheath haematoma leading to abdominal compartment syndrome. *Case Rep* 2018: bcr-2018–225936.
117. Kamath SR, Ranjit S, 2006. Clinical features, complications and atypical manifestations of children with severe forms of dengue hemorrhagic fever in South India. *Indian J Pediatr* 73: 889–895.
118. Shah I, Deshpande G, Tardeja P, 2004. Outbreak of dengue in Mumbai and predictive markers for dengue shock syndrome. *J Trop Pediatr* 50: 301–305.
119. Singhi S, Kissoon N, Bansal A, 2007. Dengue and dengue hemorrhagic fever: management issues in an intensive care unit. *J Pediatr (Rio J)* 83: S22–S35.
120. Fair BA, Kubasiak JC, Janssen I, Myers JA, Millikan KW, Deziel DJ, Luu MB, 2015. The impact of operative timing on outcomes of appendicitis: a National Surgical Quality Improvement Project analysis. *Am J Surg* 209: 498–502.
121. Papandria D, Goldstein SD, Rhee D, Salazar JH, Arlikar J, Gorgy A, Ortega G, Zhang Y, Abdullah F, 2013. Risk of perforation increases with delay in recognition and surgery for acute appendicitis. *J Surg Res* 184: 723–729.