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Frequency, Pattern and Management of Acute Abdomen in Dengue Fever in Karachi, Pakistan

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OBJECTIVE: This study aimed to determine the frequency, pattern and management of acute abdomen in patients with dengue fever.

METHODS: This descriptive case series is a prospective analysis of acute abdomen in dengue fever that was performed at three secondary care hospitals in Karachi, Pakistan from June 1, 2005 to December 31, 2008. The inclusion criterion was all patients with confirmed diagnosis of dengue fever. Patients with incomplete laboratory, ultrasound or histopathology data were excluded.

RESULTS: Among 357 patients with dengue fever, 43 (12.04%) had acute abdomen. There were 15 men and 28 women, with a median age of 29 years. These included 26 cases of acute cholecystitis, 7 cases of acute appendicitis, 7 cases of nonspecific peritonitis, and 3 cases of acute pancreatitis. Dengue hemorrhagic fever/shock syndrome was found in acute pancreatitis, and two of these patients died. Emergency surgery was required in eight patients (5 appendectomy and 3 open cholecystectomy). Substantial transfusion of blood and its components was required in eight patients who underwent emergency surgery.

CONCLUSION: Early diagnosis and prompt conservative management of dengue acute abdomen is necessary to avoid mortality and emergency surgery-related morbidity. However, if needed, surgery can be performed with acceptable morbidity. [*Asian J Surg* 2010;33(3):107–13]

Key Words: acute abdomen, appendicitis, cholecystitis, dengue fever, dengue haemorrhagic fever, pancreatitis

Introduction

Dengue virus infection has emerged as the most common flavivirus infection worldwide.[1] There are an estimated 50–100 million infections and 200,000–500,000 cases of dengue haemorrhagic fever (DHF) per year throughout the world; and the mortality rate of DHF/dengue shock syndrome (DSS) is around 5%.[1–3] The disease is endemic in tropical and subtropical regions.[4] Over the past few years, Pakistan has also emerged as a region of endemic dengue activity, the endemicity having advanced westward from India.[1] In Pakistan, the first outbreak of dengue fever (DF) was reported in 1994 in Karachi.[4] Another outbreak was encountered in the upper regions of Punjab in 2003, in addition to sporadic cases in Rawalpindi, Mangla, Peshawar, Abbottabad and Haripur.[5] There have been regular epidemics with an increasing number of dengue cases in Karachi from 2005 onward.[4–6] The ongoing developmental work in Karachi has led to the digging of many drains and roads, which has allowed water to accumulate for long periods after the monsoon rains.[1,7]

Dengue virus has four distinct serotypes (DEN1–DEN4), and infection from one serotype confers lifelong immunity to that serotype alone.[2,4,8] All serotypes are transmitted between humans by mosquitoes of the genus *Aedes*, principally *Aedes aegypti* and *Aedes albopictus*.[2,5,8] They breed in

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relatively clean rain and stagnant water in scupper drains, pots, buckets, tyres, cans and stagnant water in potted plants and the trays underneath them.[1] Post-monsoon, the hot and humid climate favours virus breeding.[6,8] This could be one reason epidemics of dengue tend to coincide with the rainy season.[2,5]

The spectrum of the disease includes DF, DHF and DSS.[4] Acute abdomen has also been reported in patients with DHF.[9] This results in challenges and difficulties with diagnosis and management. With regular dengue epidemics in Karachi, there has been an increase in the number of dengue cases that involve acute abdomen. Treatment of DF with acute abdomen remains largely supportive.

This study was conducted to determine the frequency and pattern of acute abdomen in DF patients. In addition, management guidelines were established and their effectiveness for treatment of acute abdomen in DF was noted.

Patients and methods

This descriptive case series study was a prospective analysis of patients who presented with acute abdomen and DF. It was conducted at my practice hospitals in Karachi, namely Shamsi Hospital, Atiq Medical Center and Fatima Hospital, between June 1, 2005 and December 31, 2008. Approval from the ethical committees of the above institutions was obtained. There were 357 DF patients in the series. From 413 patients initially enrolled in the study, 56 were excluded. The inclusion criterion was all patients with serologically confirmed diagnosis of DF. The exclusion criteria were: patients with incomplete laboratory, ultrasound or histopathology data, and those who were lost to follow-up. The 43 patients with acute abdomen were included for final analyses.

Informed consent was obtained from the patients after describing the nature of the study. A thorough analysis of patients' data were performed. The variables noted and analysed include hospital stay, demographic data, presenting complaint, associated complaints, comorbidity, bleeding manifestations, abdominal tenderness, acute abdomen, dengue serology, haemoglobin level, haematocrit, white blood cell count, platelet count, prothrombin time, activated partial thromboplastin time, liver function tests, serum amylase, abdominal ultrasound, chest X-ray, computed tomography (CT), management, antibiotics, transfusion of blood and its components, operative details, complications (peroperative or postoperative), histopathology report, postoperative course and follow-up for 6 months.

The serological diagnosis of DF was made on days 4–6, based on a positive immunochromatographic test (ICT) using dengue IgG/IgM rapid test (SD BIOLINE, Yonginsi, Kyonggi-do, South Korea). ICT using dengue IgG/IgM rapid test has a sensitivity of 91.2% and specificity of 90%, for both primary and secondary infection.[10] All patients with World Health Organization (WHO) criteria[11] of DHF, with or without acute abdomen, were admitted, while patients with uncomplicated DF were managed as outpatients. DHF was defined using objective evidence of plasma leakage, on the basis of haematocrit values > 45%; the criterion of a 20% increase in haematocrit for defining blood concentration was not used because there were no previous data for these patients. Acute abdomen was provisionally diagnosed on the basis of history and abdominal examination. It was defined as sudden onset of progressive abdominal pain that was the dominant feature of the patient's illness, and associated with definite peritoneal signs (e.g. tenderness and/or muscle guarding). Rebound tenderness was not attempted because it only hurts the patient and adds nothing to the diagnosis. The sites of pain and maximum tenderness help to define the aetiology of acute abdomen. The diagnosis was finally confirmed by abdominal ultrasound (e.g. oedematous and thickened gallbladder wall, appendicular wall or pancreas) and serum amylase levels in acute pancreatitis. The term "nonspecific diffuse peritonitis" was used when no definite aetiological origin of acute abdomen could be established.

The included patients with DHF and acute abdomen were divided into two groups: those who underwent emergency surgery (group A), and those who either underwent interval operation or no operation (group B). Admitted patients were placed on conservative treatment with nil by mouth and intravenous fluids. A policy of no aspirin and no nonsteroidal anti-inflammatory drugs was implemented. Proton pump inhibitor (Omeprazole) was given as prophylaxis and treatment of gastrointestinal bleeding. A decision for emergency surgery (cholecystectomy or appendectomy) was made on failure of conservative treatment after 48 hours. A policy of no antibiotics was also made, as they can increase the severity of thrombocytopenia and leukopenia; the policy was strictly followed because the cases were registered during known dengue epidemics. Only the patients who required emergency surgery were placed on prophylactic antibiotics, Cefuroxime

1.5 g intravenously at 12-hour intervals (2 doses only). Transfusions of packed red blood cells, fresh frozen plasma and platelets were required because of DHF-associated bleeding alone and/or additional emergency-operation-associated bleeding. Patients were discharged once they became asymptomatic.

Data were analyzed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Student's *t* test was applied to laboratory data to establish the statistical significance; a two-tailed p value < 0.05 was considered statistically significant. For comparison of differences between the two management groups A and B, the Pearson χ^2 test was used.

Results

Of 357 patients with DF, 276 (77.31%) had nonspecific abdominal pain (without any abdominal sign), 43 (12.04%) had acute abdomen (with definite abdominal signs), and only 38 (10.64%) had no abdominal pain. Among the 357 DF patients, there were 191 male and 166 female patients, with a mean age of 29.87 years (range: 13–72 years). Among the 43 acute abdomen cases (39 with DHF and 4 with DSS), there were 15 male and 28 female patients, with a mean age of 29.47 years (range: 15–72 years).

Table 1. Clinical features of 43 patients with acute abdomen and dengue fever

Symptom/sign	No. of patients (%)
Fever	43 (100)
Abdominal pain and tenderness	43 (100)
Right hypochondrium	26 (60.47)
Right iliac fossa	7 (16.28)
Generalised	7 (16.28)
Epigastrium	3 (6.98)
Bleeding	23 (53.49)
Surgical wound	8 (18.6)
Menorrhagia	5 (11.63)
Petechiae	4 (9.30)
Melena	3 (6.98)
Haematemesis	2 (4.65)
Gum bleeding	1 (2.33)
Nausea and/or vomiting	20 (46.51)
Rash	9 (20.93)
Muscle ache	8 (18.60)
Dizziness	7 (16.28)
Headache	6 (13.95)
Backache	5 (11.63)
Flu	3 (6.98)
Diarrhoea	2 (4.65)

The clinical manifestations of these 43 patients upon admission are summarised in Table 1. Eleven (25.58%) patients with acute abdomen had associated comorbidity: three (6.98%) with hypertension and three with diabetes mellitus; five (11.63%) patients were pregnant. Comparative analysis of laboratory findings in DF patients with and without acute abdomen is summarised in Table 2. Leukocytosis was not found in any of these patients. The patients with 10-fold elevations in serum transaminase levels tested negative for hepatitis A, B and C viruses. All patients were tested negative for malarial parasites and typhoid.

Imaging procedures performed in all 43 patients were abdominal ultrasonography and chest X-ray (erect posture). CT scanning was performed only in three patients with acute pancreatitis to assess the severity and extent of damage. The increased cost of CT scanning precluded us from using it routinely in all patients. The sonologists in the study hospitals were experienced and reliable. Diagnosis of acute cholecystitis (19 acalculous and 7 calculous cholecystitis) was made in 26 patients, acute appendicitis in seven, non-specific diffuse peritonitis in seven, and acute pancreatitis in three. In all 43 patients, presentation of acute abdomen was at 4–6 days: 31 patients on day 4, 9 patients on day 5 and 3 patients on day 6. All patients initially presented with high-grade fever, and DF was provisionally diagnosed on the basis of clinical findings and thrombocytopenia.

Eleven patients failed to improve with conservative treatment and developed diffuse peritonitis and DSS; these included five with acute appendicitis, three with acute acalculous cholecystitis and three with acute pancreatitis. Emergency surgery was performed on eight patients: five with appendectomy for perforated appendicitis and three with cholecystectomy for perforated/gangrenous cholecystitis. However, no perforation of the appendix or gallbladder was found peroperatively, although gangrenous patches were found on the gallbladder that could have become perforated. All three patients with acute pancreatitis developed adult respiratory distress syndrome (ARDS) and were placed on ventilatory support; two of these expired. Elective surgery was planned for the remaining 23 patients with acute cholecystitis (16 acalculous and 7 calculous) and two patients with acute

Table 2. Comparative analysis of laboratory data of patients with and without acute abdomen and dengue fever, at admission

Variables	Normal	Groups*	Patients outside normal range (%)	Mean	Range	SD	SEM	95% CI	
								Lower	Upper
Hb (g/dL)	10	1	51.16	9.76	6.2–14	1.401	0.214	9.275	10.137
		2	11.50	12.07	9.5–16.1	1.986	0.112	11.800	12.241
Ht (%)	< 20	1	100	43.68	22–65	10.099	1.540	40.526	46.742
		2	79.30	28.27	15.4–69.4	9.140	0.516	27.206	29.236
WBCs ($\times 10^9$/L)	4–11	1	69.77	3.73	2.5–4.9	.613	0.093	3.494	3.871
		2	59.60	3.89	1.6–7.1	1.754	0.099	3.648	4.037
Platelet count (10^9/L)	150–400	1	100	59.97	11–98	28.757	4.385	51.077	68.777
		2	88.50	77.26	17.0–193	48.274	2.724	71.854	82.574
PT (sec)	12–16	1	53.49	17.44	14–28	3.744	0.571	16.24	18.54
		2	29	16.25	13–25	3.876	0.219	15.77	16.63
APTT (sec)	32–36	1	81.4	41.16	34–58	5.420	0.827	39.44	42.78
		2	35.40	37.03	33–46	4.105	0.232	36.52	37.43
AST (IU/L)	5–40	1	100	188.81	62–478	115.330	17.588	153.27	224.26
		2	50.30	59.86	32–165	39.266	2.216	55.45	64.17
ALT (IU/L)	5–40	1	83.72	100.30	35–205	45.591	6.952	86.22	114.28
		2	21.70	36.27	21–67	11.843	0.668	34.91	37.54
ALP (IU/L)	35–130	1	53.49	127.76	42–211	42.075	6.416	114.769	140.666
		2	0	69.79	39.0–130	22.922	1.293	67.191	72.282
Total bilirubin (mg/dL)	0.2–1.3	1	34.88	1.14	0.2–3.1	.799	0.122	.848	1.340
		2	0	.58	0.2–1.2	.311	0.018	.495	.564
Amylase (IU/L)	40–140	1	23.58	195.21	45–1543	307.905	46.955	100.40	289.92
		2	0	81.24	46–134	26.523	1.497	78.25	84.14

*Group 1 includes 43 patients with acute abdomen, while group 2 includes 314 patients without acute abdomen. SEM = standard error of the mean; CI = confidence interval; Hb = haemoglobin; Ht = haematocrit; WBCs = white blood cells; PT = prothrombin time; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase.

appendicitis. At follow-up, patients with acalculous cholecystitis ($n = 16$) did not show any recurrence of abdominal features, which made scheduled surgical intervention no longer necessary. The remaining nine patients (7 calculous cholecystitis and 2 appendicitis) underwent an uneventful interval operation 6 weeks later. The decision to operate on these patients was made because of the risk of developing non-dengue recurring inflammation, according to surgical principles.

Seventeen patients experienced massive bleeding that necessitated substantial transfusions; these included eight patients who underwent emergency surgery, three with acute pancreatitis, two with acute acalculous cholecystitis, two with acute calculous cholecystitis and two with non-specific diffuse peritonitis. Only two of these had a previous history of hypertension. Transfused volumes of blood components in the 8 patients who underwent emergency operations and the 9 who did not include packed red blood cells (33 *vs.* 45 U), fresh frozen plasma (104 *vs.* 134 U) and platelets (58 *vs.* 61 MU). In addition, these patients had prolonged hospital stays (median = 12 days, range: 7–23 days) compared with other patients with acute abdomen (median = 3 days, range: 2–7 days).

Table 3 shows a comparative analysis of patients who underwent emergency (group A) and interval (group B) operations. Group A patients required more transfusions and longer hospitalization, as well as having a higher complication rate as compared with group B patients.

Discussion

The demography of DF in this series was similar to that found in other studies from Karachi, as well as from other countries.[4,5,8,12–14] Overall, male patients outnumbered

Table 3. Perioperative factors in surgical patients*

Perioperative factors	Group A, $n=8$			Group B, $n=9$		
	Mean ± SD	Frequency (%)	*p*	Mean ± SD	Frequency (%)	*p*
Transfusion						
Packed cell transfusion	4.12 ± 1.959		0.001	0.89 ± 1.537		0.121
FFP transfusion	13.00 ± 6.845		0.001	1.33 ± 2.646		0.169
Platelet transfusion	7.25 ± 2.816		0.000	1.67 ± 2.915		0.125
Hospital stay	6.50 ± 1.195		0.000	2.33 ± 1.225		0.000
Complications						
Wound haematoma		4 (50)	0.000		0	0.000
Wound infection		0			1 (11.1)	
Wound haematoma and infection		1 (12.5)			0	
No		3 (37.5)			8 (88.9)	

*Group A includes patients who underwent emergency operation, and group B includes patients who underwent interval operation. FFP = fresh frozen plasma.

females (1:0.87), but acute abdomen occurred more in females (1:1.87), similar to that found by Khor et al.[9] All patients in the present study were adults, but during the same period, another study at a paediatric hospital described paediatric DF cases.[15]

The frequency of acute abdomen in the present series was 12.04%: acute cholecystitis, 7.28% (acalculous 5.32%, and calculous 1.96%); acute appendicitis, 1.96%; nonspecific generalized peritonitis, 1.96%; and acute pancreatitis, 0.84%. Wu et al[16] have noticed acute acalculous cholecystitis in 7.63% of DF patients. Khor et al[9] have noticed acute abdomen in 4.3% patients with DHF: acute cholecystitis in 3.05% (acalculous 1.82%, and calculous 1.22%); acute appendicitis in 0.3%; and nonspecific generalised peritonitis in 0.91%. Premaratna et al[17] have reported 12 cases of acute appendicitis in DF.

WHO criteria for diagnosis of DF are fever, platelet count ≤ 100,000/mm^3 and haemorrhagic manifestations. Dengue infection can be asymptomatic or present as DF or DHF/DSS.[2,8,11] In the present series, there were 39 patients with DHF and 4 with DSS; all 43 of these patients presented with acute abdomen. Reported atypical manifestations include fulminant hepatitis, encephalopathy, cardiomyopathy, glomerulonephritis, acute pancreatitis and acalculous cholecystitis.[2,11,16,18–21] In the present series, the atypical presentations included acute cholecystitis, acute appendicitis, nonspecific diffuse peritonitis, and acute pancreatitis. However, an element of misdiagnosis was associated with nonspecific diffuse peritonitis; investigations such as oesophago-gastro-duodenoscopy, colonoscopy, CT, and laparoscopy can help to define its aetiology. These nonspecific cases can be due to acute peptic ulcer, colitis, mesenteric adenitis, or peritonism that results from dengue-associated ascites.

The exact pathogenesis in the development of acute abdomen from infection with dengue virus is unknown. It might be due to virus invasion of the gallbladder wall, appendicular wall or pancreas, which causes oedematous change.[22] All the patients with acute abdomen in the present study had DHF/DSS, therefore, the resultant plasma leakage and serous effusion with high protein content (mostly albumin) was probably responsible for oedematous and inflammatory changes in the gallbladder, appendix and pancreas. Cholestasis, spasms of the ampulla of Vater, infection, endotoxemia, microangiopathy and ischaemia reperfusion injury have been suggested by Wu et al[16] as possible pathogenic mechanisms for acute acalculous cholecystitis. The present study failed to identify any specific aetiological agent or finding on histopathology of the surgical specimens from the gallbladder and appendix, apart from gangrenous patches and lymphocytic infiltrations; appendicitis was non-purulent and bile cultures were negative. Khor et al[9] have also reported lymphocytic infiltration on histopathology of the excised appendix.

In this study the SD BIOLINE ICT test was used as the main diagnostic tool because of its low cost, availability, ease of use and rapid results. The enzyme-linked immunosorbent assay was reserved for ICT-negative, strongly suspicious

dengue cases. The WHO has reported sensitivity and specificity of SD BIOLINE of 60.9% and 90%, respectively.[23] In the present study, ICT-negative cases were also negative by enzyme-linked immunosorbent assay, thus favouring the policy of ICT. The results of ICT rapid tests obtained in this study could be attributed to the increasing experience of the laboratory technicians and pathologists involved.

Commonly associated laboratory findings with DF include thrombocytopenia, leukopenia, haemoconcentration and increased aminotransferases levels, as noted in this study (Table 2).[4,5,12–14,16,19,24] Abdominal ultrasound is a valuable tool for detecting evidence of plasma leakage and diagnosis of acute abdomen in DHF.[17,19,25,26] The reported sonographic features include thickened gallbladder wall, ascites, splenomegaly and pleural effusion.[16,25] The findings in the present study were oedematous gallbladder wall ($n = 26$) with or without calculi, oedematous appendix ($n = 7$), oedematous pancreas ($n = 3$), ascites ($n = 19$) and pleural effusion ($n = 23$). CT scanning helps in difficult cases such as acute pancreatitis.[21]

Acute abdomen in DHF can be treated successfully by conservative measures.[9,20,26] Symptomatic treatment is required for pain, fever and nausea/vomiting.[2] Patients should be well hydrated (intravenously) and receive nil by mouth.[1,11] Aspirin, nonsteroidal anti-inflammatory drugs and antibiotics should be avoided.[1,2,11] Regular monitoring is required for vital signs, platelet counts, haematocrit, fluid balance, blood gases, coagulation profile and liver function tests. Bleeding manifestations require transfusions of packed red blood cells, fresh frozen plasma and/or platelets, as did 17 patients in the present series.[2] Patients who develop ARDS need ventilatory support, as did three patients with acute pancreatitis in the present study.

Wu et al[16] have found that thickening of the gallbladder wall returned to normal, and cholecystectomy was unnecessary; however, they do recommend cholecystectomy in cases that are complicated by diffuse peritonitis. The same conservative principles were successfully used in the present study to manage acute abdomen, because the resultant bleeding tendency would have been difficult to manage during and after surgery. None of our patients received antibiotics, and only those that required an emergency operation were placed on prophylactic antibiotics. Progression to generalised peritonitis, which eventually required surgery, could not be attributed to avoidance of antibiotics because histopathology and bile cultures did not reveal any bacterial involvement. There were no predictive parameters or factors identified in the present series, which would indicate failure of conservative management in patients with acute abdomen and who were initially managed conservatively. However, all patients who underwent an emergency operation (5 appendectomy and 3 cholecystectomy) required substantial perioperative transfusion. Intraperitoneal drains in four patients did not show any significant collection, and postoperative ultrasound also showed little or no collection. Wound haematoma was the major complication in five of these patients; one of whom subsequently developed wound infection. All of them were managed by local wound care, and two required secondary wound closure. Peroperative bleeding and wound haematoma can be prevented or minimised by keeping platelet count, prothrombin time and activated partial thromboplastin time as near normal as possible. My experience in using diathermy for skin incision and dissection also helped minimise peroperative blood loss.[27] A pressure dressing can help to reduce wound haematoma. Five pregnant woman in the present series recovered completely without any consequences to the foetus or mother. DF in pregnancy can be associated with premature delivery, haemorrhagic complications during caesarean section, abruptio placentae, *in utero* foetal death, acute foetal distress during labour and mother-to-child virus transmission.[28]

In the present study, mortality in patients with acute abdomen was 4.65%, whereas there was no mortality in those without acute abdomen. Early recognition, careful monitoring and appropriate fluid therapy have decreased mortality from 40–50% to 1%.[2] Severe refractory shock, disseminated intravascular coagulation, ARDS, liver failure and neurological manifestations, singly or in combination, are the most frequent causes of death, as in the present series.[2,25]

In conclusion, patients require a high suspicion for diagnosis of DF-associated acute abdomen, and can usually be managed successfully by conservative management in the intensive care unit. Failure of improvement is an indication of disease progression, and timely surgical intervention can prevent further complications. Postoperative wound complications can be managed by local wound care.

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