



Capillary Leak Syndrome in Hospitalized Cases of Dengue Fever - Is It Really a Marker of Severity?

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Authors' contributions

This work was carried out in collaboration between all authors. Author AA is the primary consultant internist and contributed to the conception, design, draft, analysis, revision and final approval of the work to be published. Author VG was involved with data acquisition, statistical analysis and tabulation of data. Author MA contributed to revision of the manuscript, grammar and literature search for the study. All authors read and approved the final manuscript.

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ABSTRACT

Background: Dengue is a mosquito-borne viral infection spread by the *Aedes aegypti* mosquito and is caused by one of the four dengue viruses of arbovirus family. This study was undertaken to analyze detailed findings in capillary leak syndrome (CLS) among hospitalized dengue fever (DF) cases and its relation to severity of dengue illness. Since the first reported dengue fever outbreak in Madras (now Chennai) in India in 1780, recurrent outbreaks have been reported [1]. However, not many studies from India have addressed to the issue of capillary leak syndrome in these cases. This is the largest case series on 164 cases of CLS in DF.

Materials and Methods: The present study was done at Narayana Multispecialty hospital, Jaipur and had been approved by the institute ethical committee. It is a four year retrospective observational study comprising of 264 indoor patients of confirmed DF out of which 164 cases had CLS and 100 cases were without CLS. The presenting symptoms, dengue NS1 antigen and antibody tests, co-infection, co-morbidities, laboratory investigation, mortality, duration of hospital

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stay were recorded, tabulated and analyzed.

Results: Besides fever, hepato-splenomegaly, chills, vomiting, abdominal pain, body-ache, and bleeding manifestations, isolated gall bladder (GB) wall edema was present in 26 (15.9%) cases, ascites in 8 (4.9%) cases, and pleural effusion in 11 (6.7%) cases respectively. Pleural effusion was right sided in 8 (4.9%) cases, bilateral in 3 (1.8%) cases and only left sided in none of the cases. Both ascites and pleural effusion was present in 9 (5.5%) cases and triad of ascites, GB wall edema and pleural effusion was seen in 76 (46.3%) cases respectively. None of the case had pericardial effusion.

Conclusion: We conclude that CLS is as common in primary as in secondary dengue fever patients and that it probably appears to be a universal finding at microscopic level.

Keywords: Dengue fever; pleural effusion; gall bladder wall edema; ascites; capillary leak syndrome.

1. INTRODUCTION

Dengue is a complex disease. It is the most important viral disease internationally as over 50% of the world population lives in area where they are at risk of dengue and approximately 50% population lives in dengue endemic areas. In the past 50 years, the incidence of dengue worldwide has increased 30-fold, largely as a consequence of the growth of cities and increased travel. India is one of the seven countries in the South-East Asia region from where several studies have regularly reported dengue fever outbreaks, which mostly strikes in epidemic proportions often inflicting heavy morbidity and mortality [2]. India had nearly 6 million annual clinically diagnosed dengue cases between 2006 and 2012 – almost 282 times greater than the number of cases that had been officially reported [3]. Several studies have been reported on DF, DHF, DSS from different cities in India from time to time. [4-7]. All the four serotypes of the virus have been in circulation and were documented in a study from Tamil Nadu [8]. Various authors have reported CLS among these cases but studies correlating other features such as transaminitis, thrombocytopenia, hemoconcentration, hypoproteinemia with CLS are lacking. The common signs and symptoms of fever, headache, myalgia, abdominal pain, vomiting and bleeding manifestations have also been observed in other studies [4-7,9,10].

The exact clinical profile is crucial for patient management. During recent outbreaks in India, the clinical manifestations which were shown by the patients were slightly different from those in previous years [11]. The present study is an attempt to describe the salient clinical as well as laboratory findings of serologically confirmed hospitalized cases of dengue fever that had evidence of CLS. We have also tried to find out if

secondary dengue cases have more morbidity or mortality in comparison to primary dengue cases.

In DF the illness shows three phases- febrile, critical and recovery. During the transition from the febrile to afebrile phase which lasts for 2-7 days, patients without an increase in capillary permeability will improve without going through the critical phase. On the other hand patients with increased capillary permeability may manifest with the warning signs, mostly as a result of plasma leakage. The degree of plasma leakage varies from patient to patient with severe plasma leakage that leads to shock (dengue shock) and/or fluid accumulation with respiratory distress, it being considered as the marker of severity for severe dengue. We have confined ourselves to only those cases that had CLS during the critical phase of illness. It is believed that the endothelium is the target organ in severe dengue and CLS is the main complication of severe dengue.

CLS broadly is characterized by hypotension with hemoconcentration, hypoalbuminemia without albuminuria and generalized edema. However, in dengue fever elevated Hematocrit, pleural or other effusions and low protein is considered as an enough evidence of plasma leakage caused by increased vascular permeability. Generalized edema is not a feature. CLS is the principal pathologic event in causation of DHF and dengue shock syndrome (DSS).The WHO definition has retained capillary leakage as the defining lesion of most cases of severe dengue infection. The Hematocrit in CLS in DF is usually > 40%, but may be as high as 55-60%. The need to have area specific cut off values has been suggested and studies from Delhi and Chennai recommended such values [12,13]. We have taken a cut off 37.5% in our patients since we do not have our own area specific cut off [12]. This hemoconcentration is due to plasma leakage, beginning at the end of the febrile stage and

continues for one to two days after defervescence of fever. Early diagnosis of CLS is thus essential to start volume replacement and indicates progression to DSS.

We present and discuss here the findings in 164 cases of CLS in hospitalized cases of DF seen by us from January 2013 to December 2016 in our institution in Jaipur (Rajasthan), India. The fluid accumulation involved both abdomen and pleural cavities. Further, the fluid rapidly clears within a week without any specific treatment. Prognosis in CLS, in general, depends on the underlying etiology and mortality is low in CLS with dengue fever. There were only three mortality in these 164 cases of CLS in DF.

2. MATERIALS AND METHODS

The study was done in our tertiary care center. Our institutional ethics committee approved this retrospective study and informed consent was not required. The study is a four year retrospective observational study of 264 indoor patients of confirmed DF, out of which 164 had CLS and 100 were without CLS. We have included these 164 cases of CLS in the present study. It was conducted in the department of internal medicine, Narayana Multispecialty Hospital, Jaipur (Rajasthan). All these patients had critical phase of DF. Medical case record files of these cases of DF with CLS, in medical unit 1, from January 2013 to December 2016 were collected from medical records department (MRD). Demographic data, symptomatology, features of CLS, co-morbidities, co-infections, complications, dengue test report, routine laboratory investigations, ultrasonography, chest X- ray, in addition to blood and blood product transfusions and mortality data were collected, tabulated and analyzed.

Laboratory diagnosis methods available for diagnosing dengue virus infection are usually by detection of the virus, viral nucleic acid, antigens or antibodies, or a combination of these techniques. In present study diagnosis of dengue fever was done on the basis of dengue NS1 antigen and antibodies (IgM/IgG) test reports (done by dengue solid phase immunochromatographic rapid test kits for qualitative detection). Primary dengue fever (pDF) was diagnosed in cases that had either positive NS1 antigen or IgM antibodies or both. Secondary dengue fever (sDF) was diagnosed if subject had a positive NS1 antigen or IgM antibodies along with IgG antibodies or presence of all three (NS1

antigen, IgM antibody and IgG antibody). All patients given a diagnosis of DF were routinely followed-up for capillary leakage and other complications by physical examination and laboratory tests (including a complete blood count, chemistry panel and ultrasonography of abdomen, pleural cavities and pericardial space) on admission and repeated as required afterwards.

All ultrasound examinations were performed in fasting state (minimum of six hours fasting) with an ultrasound machine (GE GE Logic P6 model) using 3.5 MHz and 5 MHz probes. Gallbladder (GB) wall thickness >3 mm as measured on ultrasound were identified as positive for GB wall edema. Thoracic scanning for bilateral pleural cavities and pericardial space was done in either sitting or supine posture. Liver measuring more than 15 cm was taken as hepatomegaly and spleen measuring more than 12 cm was taken as splenomegaly. Sonographic evidence of capillary leakage was considered to be present if ascites, unilateral or bilateral pleural effusion, pericardial effusion or a thickened edematous gallbladder were present.

3. RESULTS

In all, indoor medical records of 264 cases of DF were screened. Of them 164 cases had features of CLS and were included in the study. Our results indicate that CLS is not uncommon in hospitalized cases of DF, being present in 164 (62.1%) cases. All these 164 cases of CLS were then further analyzed. There were 107 (65.2%) males and 57 (34.8%) females. The median age was 25 years in males and 31 years in females, and the female-male ratio was 1:1.9 (Table 1). The youngest and the eldest patient were of 13 years and 82 years respectively.

The result of serology tests for dengue fever (NS1, IgM, IgG antibody) are shown in Table 2. Primary DF (pDF) was seen in 133(81.1%) and Secondary DF (sDF) in 31(18.9%) cases. The clinical manifestations are mentioned in Table 3. Fever was present in almost all cases (97.6%). Other feature were hepatomegaly (65.2%), chills (54.3%) vomiting (50%) abdominal pain (53%), body-ache (41.5%), nausea (39.6%) and splenomegaly (30.5%). Headache (23.2%), bleeding manifestation (16.5%), cough (9.8%), diarrhea (11.6%), rashes (11.6%) and itching (7.9%) were not very common. Hematocrit more than 37.5% was seen in 103(62.8%) cases (Table 4). Only 11(6.7%) cases had a Hematocrit

Table 1. Number of cases with age group

S.NO.	Age category	No. of male cases	No. of female cases	Total	Percentage
1	16 -20	25	12	37	22.6
2	21-30	48	14	62	37.8
3	31-40	19	16	35	21.3
4	41-50	10	06	16	9.8
5	51-60	04	04	08	4.9
6	61-70	01	03	04	2.4
7	71-80	00	01	01	0.60
8	81-90	00	01	01	0.60
	Total	107	57	164	

Table 2. Dengue serology results

Type of dengue fever	Antigen/Antibody detected	Number of cases		Total
		Male	Female	
Primary dengue	NS1 only	85	38	123
	IgM only	02	02	04
	NS1+IgM	04	02	06
	Total			133 (81.1%)
Secondary dengue	NS1+IgG	07	05	12
	IgG and IgM	04	02	06
	NS1, IgM ,IgG	05	08	13
	Total			31 (18.9%)

of >50%. Hypoalbuminemia was seen in 75 (45.7%) cases (Table 4). It was moderate to severe in 62(37.8%) cases. Transaminitis – raised aspartate transaminase (AST) was seen in 160(97.6%) cases and alanine transaminase (ALT) in 145(88.4%) cases respectively (Table 4).

Thrombocytopenia was present in all cases (Table 5) being mild in 9(8%), moderate in 10(6.1%) and severe in 145(88.4%) cases. Bleeding manifestation was present in 27 (16.5%) cases, menorrhagia being the commonest. Therapeutic platelet transfusions were given in only 23(14%) of these cases who had associated significant bleeding manifestation. Lowest platelet count was 3×10^3 /cmm. Severe critical thrombocytopenia ($<20 \times 10^3$ /cmm.) was seen in 96(58.5%) cases. One patient with platelet count 77×10^3 /cmm had severe life threatening post partum hemorrhage [14].

Sites of plasma leakage in these 164 cases are mentioned in table 6. Polyserositis (ascites, GB wall edema and right sided or bilateral pleural effusion) was seen in 76(46.3%) cases. Isolated GB wall edema was seen in 26(15.9%), ascites and pleural effusion in 22(13.4%) and isolated left or bilateral pleural effusion in 11(6.7%) cases respectively. None of the cases had only left side pleural effusion or pericardial effusion.

Table 3. Distribution of dengue cases with CLS according to clinical manifestation

Clinical manifestations	No. of cases (%)
Fever	160 (97.6)
Hepatomegaly	107 (65.2)
Chill	89 (54.3)
Vomiting	82 (50.0)
Abdominal Pain	87 (53.0)
Body-ache	68 (41.5)
Nausea	65 (39.6)
Splenomegaly	50 (30.5)
Weakness	34 (20.7)
Loss of Appetite	28 (17.1)
Headache	38 (23.2)
Bleeding	27 (16.5)
Diarrhea	19 (11.6)
Cough	16 (9.8)
Rashes	19 (11.6)
Itching	13 (7.9)

Table 7 show co-morbidities, co-infection, medical intensive care unit (MICU) admissions and mortality in these 164 cases. Co-morbidities such as diabetes mellitus, hypertension, coronary artery disease, chronic obstructive pulmonary disease(COPD), benign prostate hyperplasia requiring indwelling catheterization were seen in 24(14.6%). Co-infection was seen in 07(4.3%) cases. It was Scrub typhus in 4 cases, *plasmodium vivax* malaria in 1 case and *plasmodium falciparum* malaria in 2 cases

respectively. MICU admissions were required in 28(17.1%) cases. There were 3(1.8%) mortality. All mortality cases had primary dengue fever (NS1 antigen positive). The first mortality case was an elderly 70 years male, post CABG case and had fever along with soakage/bleeding from surgical site in fifth week after surgery. He had thrombocytopenia, hypotension, adult respiratory distress syndrome, and acute kidney injury, severe transaminitis (AST 8400 IU/L and ALT 5329 IU/L) along with features of CLS. The second case was of a 40 years female who presented with fever and painful abdomen. She had biochemical and ultrasound evidence of acute pancreatitis, transaminitis, hemoconcentration and thrombocytopenia with lowest platelet count of 11×10^3 /cmm. She had sudden death after 10 hours of admission. The family refused for autopsy to be performed on her. The third patient was a 25 year male who also had fever with pain in the abdomen. He had acute pancreatitis, severe transaminitis (AST 19450 IU/L, ALT 6838 IU/L), mild jaundice, bleeding (melena), thrombocytopenia and CLS. All three of them were given blood and blood products transfusion as needed. Rest of the patients had a favorable course.

It was observed that the 31(18.9%) cases with sDF were not more symptomatic than pDF cases. The average hospital stay duration was 4-6 days among whom 152(92%) cases had a stay of less than one week (Table 8).

Table 9 show incidence of CLS in primary and secondary dengue fever cases. The results were not statistically significant ($P > 0.05$). This suggests that CLS in pDF was as commonly found as in sDF. Table 10 show salient clinical and laboratory features in CLS and non CLS group. It was found that hepatosplenomegaly; bodyaches, abdominal pain, severe thrombocytopenia and raised serum aspartate transaminase were more common in CLS group. The results were statistically significant ($p < 0.05$). This means that patient who have these features should be closely observed and monitored for development of CLS and managed accordingly to prevent development of DHF/DSS.

4. DISCUSSION

Dengue virus infection ranges from a mild febrile illness to severe illness. Severe dengue is mainly characterized by transient plasma leakage, which may lead to a sudden onset of shock around the end of febrile phase of illness. Severe bleeding

and organ impairment as compared to CLS are less common features of severe dengue. The capillary leakage is considered to be present if any of the following three features are present: (1) a rise in the Hematocrit equal to or greater than 20% above average for age, sex and population; (2) a drop in the Hematocrit following volume replacement treatment equal to or greater than 20% of baseline; and (3) signs of plasma leakage such as pleural effusion, ascites and hypoproteinemia [15,16]. Of these, hemoconcentration is a retrospective parameter and rarely of clinical benefit. Hypoalbuminemia is not seen frequently and clinical recognition of plasma leakage is a difficult sign. Thus, clinically it is difficult to predict which dengue patient will develop severe complications. In our case series a Hematocrit of >40 was seen in 81 (49.4%) cases and when area specific cut off value (37.5%) is taken into consideration the number rises to 103(62.8%) as was done in a Chennai based study [12]. Unfortunately we did not have any area specific cut off from this part of the country and for our study we have considered the value from Chennai based study. Hypoalbuminemia (< 3.2 gm/dl) was seen in 75(45.7%) cases suggesting that it is an infrequent finding. In contrast, ultrasonography can directly visualize plasma leakage and Thoraco-abdominal ultrasonography is a highly accurate method for assessing even small amounts of pleural effusion, ascites, pericardial effusion and GB wall edema. It has a sensitivity of nearly 100% and is even recommended by the 2009 WHO guidelines as a suitable tool for assessing CLS [17,18,19]. Thus, instead of a rise in Hematocrit and hypoalbuminemia, Thoraco-abdominal ultrasonography is an important tool to pick up CLS early in adult dengue fever patients. It picked up 164 cases among 264 cases of DENF.

The WHO classification (2009) defines severe dengue infection in case plasma leakage leading to shock or respiratory failure, severe bleeding or severe organ failure is present. However, as seen in this study also, in clinical practice severe bleeding and severe organ failure are relatively uncommon and rarely occur without plasma leakage. Hence, plasma leakage is an essential element of severe dengue, regardless of any classification. Various studies have demonstrated that among hospitalized patients with uncomplicated DF, the prevalence of Sonographic capillary leak ranges from 34% [18,19] to as high as 100% [5]. It was 164(62.1%) in our series of 264 DF cases.

Table 4. Hematocrit, albumin and transaminases

Hematocrit(%)		Hypoalbuminemia (mg/dl)		AST / SGOT(IU)		ALT / SGPT(IU)	
Test value	No. of cases (%)	Test value (Normal \geq 3.3)	No. of cases (%)	Test Value (15-37 IU/L)	No. of cases (%)	Test value (30-65 IU/L)	No. of cases (%)
37.5-40.0	22 (13.4%)	3.2-3.0(mild)	13 (7.9%)	38-74 (1-2 XULN)	5 (3%)	66-130 (1-2 XULN)	55 (33.5%)
40.1-50.0	70 (42.7%)	2.9-2.5(moderate)	46 (28%)	75-185 (2-5X ULN)	53 (32.3%)	131-325 (2-5X ULN)	73 (44.5%)
50.1-60.0	11 (6.7%)	< 2.5(severe)	16 (9.8%)	\geq 186 (>5XULN)	102 (62.2%)	\geq 326 (>5XULN)	17 (10.4%)

AST/SGOT: Aspartate transaminase/serum glutamic-oxaloacetic transaminase

ALT/SGP: Alanine transaminase/Serum glutamic pyruvic transaminase

Table 5. Thrombocytopenia, hemorrhage and platelet transfusions

Platelet count ($\times 10^3$ /cmm)	Total cases (n=164)	Bleeding cases	Therapeutic transfusions	Prophylactic Transfusion
<20	96	18	18	47
20 – 50	49	08	04	08
50 -100	10	01	01	00
100-150	09	0	00	00

Table 6. Site of capillary leak

Site of capillary leak	No. of cases (%) (n=164)
Ascites + GB wall edema + Pleural effusion	76 (46.3)
Only GB wall edema	26 (15.9%)
Ascites + GB wall edema	22 (13.4)
Ascites + Pleural effusion	09 (5.5)
Only Ascites	08 (4.9)
Isolated Right side pleural effusion	08 (4.9)
Bilateral pleural effusion	03 (1.8)

GB: Gall bladder

Table 7. Incidence of co-morbidity, co-infection, MICU admission and mortality in CLS dengue cases (n=164)

	Male	Female	Total (%)
Co-morbidity	17	07	24 (14.6)
Co-infection	04	03	07 (4.3)
MICU admission	20	08	28 (17.1)
Mortality	02	01	03 (1.8)

Table 8. Hospital stay duration

Duration of stay in hospital in days	No. of cases (%)
1-3 days	44 (26.8)
4-6 days	107 (65.2)
7-9 days	10 (6.1)
10-12 days	2 (1.2)
13-15 days	1 (0.6)
Total Patients	164

In our case series of 164 cases of CLS, 133(81.1%) had pDF and 31(18.9%) had sDF. CLS was as frequently seen in pDF as in sDF. The mechanism that underlies capillary leakage in DF remains undefined. Vascular endothelial growth factor (VEGF), a potent permeability enhancing cytokine, has been thought to play a pivotal role in mediating plasma leakage in DHF. During the critical phase, higher levels of Galectin-9(Gal-9) had been reported during the critical phase of dengue virus infected patients compared to healthy or those with non-dengue febrile illness and the highest Gal-9 levels were observed in DHF. Numerous cytokines and chemokines had been found elevated in dengue virus infection and were associated with Gal-9 levels. [18] Another mechanism is antibody dependent enhancement i.e., immune enhancement of viral replication because of

previous exposure to dengue virus as a cause of capillary leakage/severe disease. Studies in travelers from non endemic countries have shown that capillary leak is more likely to represent a fundamental mechanism of disease in dengue virus infection, regardless of the host immune status. Meltzer et al suggested that secondary infection is not a prerequisite condition for development of capillary leak in dengue infection and does not increase the risk for severe disease among travelers with dengue infection [19]. In this case series we have also observed that secondary dengue infection is not a must for plasma leakage or increased severity of dengue infection. It was seen that CLS among subjects with primary dengue infection was as common as in secondary dengue infection cases. The importance of immune enhancement caused by secondary infection as the only cause of capillary leakage in DF thus needs to be reevaluated. It is possible that CLS may even be a universal finding at microscopic level [19]. It appears that several factors including pathogenicity of specific viral serotype, virulence of the circulating virus, immunological responses, higher levels of viral loads and NS1 proteins, VEGF, Gal-9 and other cytokines are all implicated in a complex manner for the appearance of CLS /DHF in cases with DF.

In CLS collection of fluid frequently involves multiple sites. In our series, Polyserositis (GB wall edema + ascites + pleural effusions) was seen in 76(46.3%) cases, followed by GB wall edema in 26(15.9%) cases, and ascites + GB wall edema in 22(13.4%) cases respectively. None of the cases had left side pleural effusion or pericardial effusion. Similar findings were noted in others studies also [20,21,22]. The fluid accumulation was mild to moderate in our case series and none of our cases required aspiration. It cleared within a week and no specific treatment was required.

Scrub typhus and malaria co infection with dengue fever has been reported in many studies [23,24,25]. We had 7 (4.3%) cases with dual infection and all of them recovered. Four of them had co infection with scrub typhus. Malaria co-infection was seen in 3 cases. Two of them had *Plasmodium falciparum* and one *Plasmodium vivax* co-infection respectively. One of these cases also developed secondary hemophagocytic lymphohistiocytosis syndrome [26]. Persistence of fever, moderate to severe

Table 9. CLS and non CLS cases with pDF and sDF

Parameter	CLS group (%) (n=164)	Non CLS group (%) (n=100)
Number of cases with Primary Dengue fever(n=219)	133 (81.1)	86 (86)
Number of cases with Secondary Dengue fever(n=45)	31 (18.9)	14 (14)

CLS: capillary leak syndrome; pDF: primary dengue fever; sDF: secondary dengue fever
 $\chi^2 = 1.056$, $df = 1$, $\chi^2/df = 1.06$, $P(\chi^2 > 1.056) = 0.3042$
 The chi-square statistic is 1.0559. The p-value is .304156. This result is not significant at $p < .05$

Table 10. Salient clinical and laboratory features of CLS and non CLS cases

Parameter	CLS group (%) (n=164)	Non CLS group (%) (n=100)
Abdominal pain	87 (53)	35 (35)
Hepatomegaly	107 (65.2)	17 (17)
Splenomegaly	50 (30.5)	16 (16)
Body-ache	68 (41.5)	32 (32)
Cases with Severe Thrombocytopenia (platelets count $< 50 \times 10^3$ /cmm)	145 (88.4)	66 (66)
Raised AST (AST > 37 U/L)	160 (97.6)	78 (78)

CLS: Capillary leak syndrome; AST: Aspartate transaminase
 $\chi^2 = 17.483$, $df = 5$, $\chi^2/df = 3.50$, $P(\chi^2 > 17.483) = 0.0037$
 The chi-square statistic is 17.483. The p-value is .0037. This result is significant at $p < .05$

transaminitis with cholestasis, presence of an eschar, multi-organ involvement should caution clinicians to suspect co-infection.

Little is known about dengue in the elderly [27]. A surveillance study [28] showed that clinical manifestations of dengue in the elderly are similar to those of younger adults. In our case series we had 10 cases of DENF in elderly (>60 years age). Of them 6 cases had CLS and did not differ from other cases in their clinical manifestations and outcomes. Only one of them who had undergone CABG and had multiple co morbidities died following severe DHF.

Our study has some limitations. Ours being a tertiary centre selection bias is expected as usually severe cases are being referred to such centres. Serial ultrasounds were not done from the first day of infection in these patients as most of them were referred cases and the first ultrasound was done within 24 hours of admission. We cannot comment on the day of illness at which plasma leakage could have started. Nevertheless our results have reproduced a high prevalence of capillary leakage in hospitalized adult patients during critical phase of primary as well as secondary DF.

5. CONCLUSIONS

One of the most important challenges for clinicians who see dengue patients is to identify

patients who will progress to severe disease. Hematocrit is determined by tracking changes in serial Hematocrit measurements and hypoalbuminemia is infrequent. Both are insensitive indicators of CLS compared to ultrasonography. In absence of accurate biomarkers, presence of plasma leakage can pick up such cases early in critical phase. USG thus helps to identify dengue patients at risk for shock.

We suggest early ultrasonography for CLS in hospitalized patients (and even if not hospitalized) who have marked bodyaches, pain abdomen, hepato-splenomegaly, severe thrombocytopenia, and raised AST.

Capillary leakage in pDF is as common as in sDF and thus we feel that the probable pathogenesis of DHF or DSS which is considered due to enhanced immune mediated platelet destruction with release of cytokines and activation of the complement system leading to capillary leak syndrome needs to be re-evaluated. Clinicians who treat dengue fever should have a high index of suspicion for co-infection in cases with inadequate or failure of therapeutic response.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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