ORIGINAL ARTICLE

# FLUID REPLACEMENT IN CHILDREN WITH DENGUE AND FACTORS ASSOCIATED WITH PULMONARY EDEMA

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**Abstract**

**Objective:** To determine fluid replacement and factors associated with pulmonary edema in children with dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS).

**Methods:** This study was conducted over a period of 1 month in 32 children with DHF/DSS and a positive Dengue IgM capture ELISA. Intravenous (IV) fluid therapy was indicated when patient had hemoconcentration, poor capillary refill time, decreased urine output and/or hypotension or when child was unable to take orally. Fluids were adjusted according to the clinical condition, urine output and hematocrit. Statistical analysis was done to determine, complications of fluid therapy and factors associated with pulmonary edema.

**Results:** Mean age at presentation was 6 years with male:female ratio of 1:1. Fluids were given for an average of 52.1±34.6 hours in 30 patients. Two children did not require IV fluids as oral intake was satisfactory. Average fluids given were 2893.8±2838.2 ml with median of 1975 cc. Total fluids per kilogram of body weight were 143.7cc/kg±103.5 cc/kg. The urine output on Day1 of hospitalization was 2±0.7cc/kg/hour which increased to 4.9±1.9cc/kg/hour. Pulmonary edema was seen in 9 children (28%) and was related to more hours of intravenous fluids (82±41.4 hours Vs 39.3± 22hours; p=0.0009), more quantity of fluid (4649.7cc±3775.3cc Vs 2206.7±2100.7cc; p=0.06). All children with pulmonary edema had shock initially (p=0.0018). However there was no difference in time interval to recovery in children with/without pulmonary edema (p=0.134). Two children had acute respiratory distress syndrome (ARDS) which was not related to fluids, pulmonary edema and shock. Thirty one (97%) children recovered with average recovery time of 5.8±3.5 days and 1(3%) died.

**Conclusion:** Longer duration of fluid therapy and larger quantity of fluids can lead to pulmonary edema. Pulmonary edema is seen in patients with DSS. Thus judicious management of fluids and DSS is required to minimize complications of fluid overload states.

## Introduction

Volume replacement is the mainstay for treatment of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). (1) World Health Organization (WHO) guidelines for volume replacement are based on studies of DHF/DSS in children and early and effective replacement of plasma loss with crystalloid, colloidal solutions results in favorable outcome in most patients. (1) However volume replacement in children with dengue is a challenging management problem with very few published studies on the same (2) with no large studies to determine the optimal fluid regimen though there have been studies that have compared use of crystalloid and colloids as replacement fluids. (3,4) Maintenance of perfusion to vital organs remains the objective behind volume replacement, however risk of fluid overload always remains. About 8% of patients may go into fluid overload during convalescent phase of illness due to absorption of extravasated plasma from the interstitial compartment. (2) We undertook this study to determine the optimum fluid requirement in children with dengue and also to determine the factors associated with fluid overload state.

## Methods & Materials

This prospective study was done over a period of 1 month in August 2007. Thirty-two children who presented with either DHF or DSS were included in the study. A thorough clinical examination and detailed history was taken in each child. Each child was confirmed to have dengue by a positive dengue IgM capture Elisa test. Those patients with negative dengue IgM tests were excluded from the study. On admission, a venous blood sample was obtained for complete blood count, hematocrit, liver transaminases, renal function tests, coagulation profile. Chest radiograph, echocardiography and tests for other infections such as Leptospira IgM, Optimal for malaria, blood culture were done as and when required. Intravenous fluids were indicated when the patient had one or more of the signs/symptoms: hemoconcentration, hypotension, oliguria or poor capillary refill time. Normal saline was started at a rate of 4ml/kg/hour and then adjusted accordingly to pulse, urine output, capillary refill time and blood pressure. The goal of the IV fluid was to maintain the blood pressure at the lower normal range, urine output between 1-1.5ml/kg/hour and a normal capillary refill time. For patients with DSS, initial bolus of ringer lactate (RL) at 20ml/kg over 1 hour was followed by a fluid rate of 10ml/kg/hour which was then adjusted as per the above criteria. A blood transfusion was indicated only in patients with severe bleeding. Intravenous fluids were stopped when the patient's condition was stable for more than 24 hours or there was any sign/symptom of fluid overload. For those who developed fluid overload, furosemide was given at 0.5-1mg/kg/dose. Frequency and urine output volume was recorded every 4 hours. A fluid balance sheet was also used to record the type, rate and quantity of fluid administered and to calculate the amount of intravenous fluid (IVF) per kg body weight per 24 hours.

**Statistical analysis:** The outcome measures were the total volume of intravenous fluids infused; duration of intravenous fluid therapy, development of any complications related to fluid therapy. The outcome measures were analyzed for associated factors such as gender, biochemical parameters, complications such as acute respiratory distress syndrome (ARDS), pulmonary edema and shock using t test and chi square test. A p value of $<0.05$ was considered statistically significant.

## Results

Clinical and laboratory findings are shown in Table 1. The mean age of patients was 6.1+3.9 years

**Table 1a: Clinical and laboratory findings of children with DHF/DSS**

| Parameter | Mean ± SD |
|---|---|
| Fever (days) | 7.7 ± 4.9 |
| Platelets (cells/cumm) | 105100 ± 75600 |
| SGOT (IU/L) | 182.6 ± 278.3 |
| SGPT (IU/L) | 84.9 ± 121.4 |
| PTT (sec) | 46.5 ± 27.1 |
| PT (sec) | 15.4 ± 3.0 |
| Packed cell volume | 34.5 ± 7.2 |
| Hemoglobin (gm/dl) | 10.9 ± 2.5 |
| White cell count (cells/cumm) | 7830 ± 4310 |

**Table 1b: Clinical and laboratory findings of children with DHF/DSS**

| Parameter | N (%) |
|---|---|
| Fever (days) | 32 (100%) |
| Thrombocytopenia | 25 (78.1%) |
| Elevated SGOT | 26 (81.5%) |
| Elevated SGPT | 24 (75%) |
| Prolonged PTT | 21 (65.6%) |
| Prolonged PT | 18 (56.5%) |
| Hypotension | 18 (56.5%) |
| Hemoconcentration | 14 (43.7%) |
| Rash | 8 (25%) |
| Malena | 10 (31.3%) |
| Leucopenia | 6 (18.8%) |
| Leucocytosis | 5 (15.6%) |

**Table 2: Clinical and Laboratory parameters with fluid therapy**

| Factors | N | Fluid (hours) | P value | Fluids (cc/kg) | P value |
|---|---|---|---|---|---|
| **Sex** | | | | | |
| Male | 16 | 58.4 ± 44.2 | 0.53 | 149.5 ± 129.5 | 0.75 |
| Female | 16 | 48.4 ± 24.4 | | 138 ± 72.9 | |
| Location | | | | | |
| Central Mumbai | 14 | 57.9 ± 40.9 | 0.4 | 178.5 ± 103.3 | 0.36 |
| Central suburbs | 5 | 45 ± 15.1 | | 118 ± 86.6 | |
| Western Mumbai | 11 | 54.6 ± 30.5 | | 125 ± 109.2 | |
| Outstation | 2 | 14 ± 19.8 | | 68.5 ± 96.8 | |
| Rash | 8 | 65.8 ± 54.3 | 0.19 | 184 ± 124.3 | 0.21 |
| Malena | 10 | 61 ± 49.4 | 0.33 | 157 ± 129 | 0.63 |
| Thrombocytopenia | 24 | 54.7 ± 36.2 | 0.43 | 158.6 ± 99.5 | 0.12 |
| Leucopenia | 6 | 68 ± 53.3 | 0.21 | 197.3 ± 124.4 | 0.16 |
| Leucocytosis | 4 | 50.5 ± 24.8 | 0.92 | 74.2 ± 79.2 | 0.1 |
| Hemoconcentration | 14 | 64.3 ± 42.3 | 0.09 | 180.4 ± 113 | 0.09 |

with median of 7 years and range of 9 months to 12 years. Male: female ratio was 16:16. Fourteen children (43.8%) were located from Central Mumbai, 11 (34.4%) were from western suburbs, 5 (15.6%) were from central suburbs and 2 (6.2%) were from out station. Two (6.2%) patients had co-infection with malaria (one each had vivax and falciparum malaria) whereas 1 (3.1%) was co-infected with leptospirosis. Thirty (93.8%) required IVF therapy whereas 2 patients improved with oral intake of fluids. Twelve patients (37.5%) required RL boluses. The mean fluids given were 143.7±103.5cc/kg with median of 136.5cc/kg. Total duration of fluids required were for 52.1±34.6 hours with median of 48 hours. Urine output at start of fluid therapy was 2±0.7cc/kg/hour which increased to 4.9±1.9cc/kg/hour on recovery. Seven (21.9%) patients required ionotropes whereas 6 (18.8%) patients required plasma transfusion and 5 (15.6%) patients each required blood and platelet transfusion. Thirty one (97%) patients recovered with average recovery time of 5.8±3.5 days and one patient (3%) died. Two patients (6.2%) each had ARDS and renal failure. Pulmonary edema was seen in 9 (28%) patients.

Factors affecting fluid therapy duration and volume are depicted in Table 2. There was no difference in fluid therapy per gender, location of residence, clinical and laboratory parameters. Patients with shock required more fluids as compared to those without shock (201.9±95cc/kg vs. 68.9±54.9cc/kg; p <0.0001) and those with pulmonary edema also received more total fluids as compared to those without pulmonary edema (4649.7±3775.3 cc vs. 2206.7±2100.7 cc; p=0.026). Patients with pulmonary edema also received longer duration of fluids (82±41.4 hours vs. 39.3±22 hours; p=0.0009) and those with shock also received longer duration of fluids (67.9±33.8 hours vs. 28.5±19.7 hours; p=0.0011). Fluid therapy volume (p=0.63) and duration (p=0.06) had no relation with ARDS. Pulmonary edema was seen in 9 out of 18 patients (50%) with shock (p=0.002) and all these patients received fluids for more than 48 hours (p=0.03). However in patients with pulmonary edema, there was no difference in number of days to recovery (7.4±5.3 days, p=0.134).

**Discussion**

About 25 years ago, treatment of dengue with intravenous fluid replacement led to decrease in mortality from 20% to 2%. (5) In 1974, WHO recommended ringers lactate or isotonic saline solution for quick infusion and colloids 10-20 ml/kg/h to be substituted only in cases of profound shock. (6) Nimmanitya et al reported 487 cases of dengue shock syndrome out of which 61% were successfully treated with crystalloids (ringers lactate/acetate), 22% with colloids (dextran 40%) and 15% required blood transfusion. (7)

In management of patients with DSS, it is difficult to correct hypovolemia rapidly without volume overload. All infants must be treated as high-risk patients who require early intervention with colloids, as in older children with grade IV disease. (2) There has been much debate about the optimal means of fluid replacement in a number of diverse conditions, but there are no specified recommendations as such. (8) In several studies of patients with DSS, hemodynamic profile is stabilized faster with colloids than compared to crystalloids, Also they require less resuscitation volumes than crystalloids. Also crystalloids have shown an increase incidence of acute respiratory distress syndrome .because they have a considerable shorter intravascular resistance time than colloids and may precipitate pulmonary edema if the pulmonary microcirculation is also affected by systemic increase in capillary permeability. (9) Conversely there are also reports of increased mortality associated with usage of colloids (10) and vice versa. (11) There have been several autopsy cases of fatal dengue where pulmonary edema has been seen following excessive fluid resuscitation. (12) The cause of acute respiratory failure in DHF patients is usually caused by the administration of intravenous fluids too rapidly or for too long a period. Lum et al described acute respiratory distress syndrome in three patients with DHF with prolonged shock and tissue hypoxia when crystalloids were administered too rapidly. (13)

Colloids have a longer intravascular residence time than the crystalloids, and by increasing the colloid osmotic pressure, they may draw extravasated fluid back into the intravascular compartment. It has been estimated that 2–4 times the volume of crystalloids may need to be infused to achieve the same degree of resuscitation as in colloids. (14) However, in DSS the extra volume of crystalloid required to achieve adequate cardiovascular stability may exacerbate the ongoing fluid leakage and precipitate pulmonary edema. Although DHF in infants comprise less than 5% of all cases still mortality is more in infants compared to others. (15) The management of DSS is a balancing act between adequate resuscitation and overzealous replacement, often in circumstances where full monitoring cannot be done. (5) The present study emphasizes that intravenous fluids must be administered with special care to avoid fluid overload and thus pulmonary edema. This involves following established procedures for use of colloidal solutions and blood transfusions. Special emphasis needs to be given to infants with DHF/DSS who have developed severe complications like pulmonary edema.

**Funding :** None

**Conflict of Interest :** None

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**DOI :** 10.7199/ped.oncall.2017.45