Original Article

Respiratory Distress Associated with Dengue Hemorrhagic Fever on Paediatric Patients: Learning from a Provincial Hospital in Southern Vietnam

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Abstract

Introduction: Respiratory distress is serious issue in dengue hemorrhagic fever (DHF), especially in children. Appropriate and timely intervention for treatment of respiratory distress is a prerequisite for treatment success; however, this requires appropriate preparation of personnel and equipment. Therefore, further research is needed on the rate, the associated factors, and the severity of respiratory distress. **Objective:** The aim of this study was to investigate DHF treatment in a provincial pediatric hospital in southern of Vietnam. **Methods:** This was a cross-sectional study conducted between January 2015 and June 2017 at Dongnnai Paediatric Hospital (DPH). All DSS cases treated at DPH in the study period were invited to participate in the study. The NS1 rapid test, combined with an IgM test, was used to indicate DHF. Results: In total, 1,085 pediatric patients were admitted to DPH, and 800 of them developed dengue shock syndrome (DSS); the mortality rate was 0.3%. The average age of DSS patients was 9.3 ± 3 years. A total of 137 patients (17.1%) suffered from respiratory distress. The onset of respiratory distress was 23.6 hours after resuscitation with fluid, and 76.3% of these patients received respiratory support with nasal continuous positive airway pressure (CPAP). Mechanical ventilation was required in 5.9% of patients; the shortest time of mechanical ventilation was 1.5 days and the maximum were 13 days. The epidemiology, signs, and treatment of respiratory distress are associated with many factors, including age, mucosal hemorrhage, hematocrit (Hct), albumin, blood lactate at shock, total fluid volume, molecule fluid volume, number of hours of infusion, amount of urine during infusion, and rate of re-shock. **Conclusion:** The respiratory failure in children with DSS has a rate of 17.1%, is mostly at the moderate level, and requires CPAP. Young age, high plasma loss, re-shock, and the volume of parenteral administration are factors that contribute to respiratory distress in pediatric DHF cases.

Keywords: NCPAP, oxygen therapy, pediatrics, parenteral administration, shock syndrome, Vietnam

Introduction

Dengue is an acute fever caused by 4 types of dengue virus. An estimated three billion people worldwide live in areas at risk for this disease. Annually, 390 million new cases and 20,000 deaths are reported due to dengue.[1] The disease is steadily increasing, with Southeast Asia having the highest incidence rate globally.[2] In Vietnam, studies have been conducted to evaluate the economic impact of dengue hemorrhagic fever (DHF) on health systems. The results indicated an economic burden of US$ 37,686 in 2015,[3] with the average cost per case at US$ 139.3 ± 61.7 in 2016.[4]

Previous community-oriented studies have also explored the practical competency toward dengue and dengue prevention.[5-7] The lack of readily available medications means that fluid therapy is the only management procedure for dengue infection.[8] However, the recent development and testing of dengue vaccines are now indicating a new approach for dengue prevention.[9] The populace in southern Vietnam has shown a high willingness to pay for dengue vaccines (DV), which range in cost from US$ 86.96 to US$ 217.39 for a three-dose scheme, and this support will advance the introduction of DV in Vietnam.[10]

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The main causes of mortality in DHF are prolonged shock, respiratory distress, severe coagulopathy, and organ failure (e.g., the liver or kidneys). Respiratory distress is a challenge in treating dengue shock syndrome (DSS) because it has many contributing factors, including pleural effusion, peritoneal, increased permeability of the lung parenchyma, metabolic acidosis, and cognitive disorders.[2] Children with DHF who have respiratory distress are much more difficult to treat than are adult patients. Administering too much fluid may cause respiratory failure, but a lack of fluids may cause a lasting shock. The treatments also vary depending on the cause of the respiratory failure, while the treatments themselves can contribute to extremely serious complications in children with DHF. Therefore, good control of respiratory distress is essential for the successful treatment of DHF. Respiratory distress in pediatric patients with DF commonly arises due to pleural effusion and peritoneal and capillary alveolar lesions.

Vietnam is one of the Southeast Asian countries with a high annual incidence of DHF.[8] During the epidemic season, the number of DHF cases in children is very high and poses a challenge to district and provincial hospitals, as treatment is greatly dependent on the preparation and experience of the physician. In this context, if the hospitals ensured adequate training and provided oxygen equipment, such as continuous positive airway pressure (CPAP) masks and ventilators, the treatments would be more successful.

The aim of this study was to investigate the DHF treatment used in a provincial pediatric hospital in southern Vietnam. We explored the ratio of respiratory distress among DSS cases and identified factors associated with respiratory distress in pediatric patients.

Materials and Methods

Study design and study site

This was a cross-sectional study conducted between January 2015 and June 2017 at Dongnai Paediatric Hospital (DPH). Dongnai is an industrial province located to the east of Ho Chi Minh City. DPH is the largest health facility that specializes in pediatric medicine in the province.

Term definitions

In this study, we defined children as patients aged 16 years or younger (according to Vietnamese Law of Children No.102/2016/QH13).[11] DHF was indicated based on blood tests with positive immunoglobulin M (IgM).[8] DSS was diagnosed based on the WHO guidelines, version 2009.[8] Respiratory distress syndrome (RDS) was diagnosed if the patient suffered from at least one of the following: i) tachypnea, ii) use of accessory muscles for respiration, iii) cyanosis, or iv) peripheral oxygen saturation (SpO_2) lower than 95%. RDS cases were categorized into three levels (**Table 1**). Pleural effusion was also categorized based on the pleural effusion index (PEI) determined from lung X-rays [12].

Table 1. RDS determination and categorization

Standard to determine RDS	Level of RDS		
	Mild	Moderate	Severe
Tachypnea			
- patient under 12 months of age: ≥50 (br/			
- patient 12 months to 5 years old: ≥40 br	✓	✓	✓
- patient 5 to 12 years old: ≥30 br/mir			
- patient 12 to 16 years old: ≥25 br/mi			
Use of accessory muscles for respiration		✓	✓
***Cyanosis* (bluish and purplish discoloration due to low oxygen saturation)**			✓
SpO_2 was lower than 95%			
- Higher than 90 to 95%		✓	
- ≤90%			✓

Abbreviation: br/min, breaths per minute; RDS, respiratory distress syndrome; SpO_2, peripheral oxygen saturation.

Data collection

All DSS cases treated at DPH during the study period were invited to participate in the study. The exclusion criteria were: i) unwillingness to participate, ii) pre-treatment at other health facilities prior to DPH admission, iii) respiratory distress occurring before diagnosis of DSS, and iv) congenital heart or respiratory disease.

Sub-clinical laboratory tests

The NS1 rapid test, combined with an IgM test, was used to confirm DHF. The NS1 test was obtained from AVANTA DIAGNOTICS Test Co., Ltd., and the IgM antibody capture enzyme-linked immunosorbent assay (MAC ELISA) method was used to conduct the IgM test. In addition to the DHF tests, blood samples were collected for complete blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, creatinine, bilirubin, arterial-blood gas, and coagulation determinations.

Data analysis

Microsoft Excel was used to conduct descriptive statistics. The data had a normal distribution, so the t-test and chi square test were used to compare variables among the groups of patients. A p-value less than 0.05 was considered statistically significant.

Ethical approval

The study protocol was approved by the Council of Medical Ethics at DPH. The participants were provided a clear explanation about the research purpose, and all interviews were voluntary.

RESULTS

Characteristics

From January 2015 to June 2017, 1,085 pediatric patients with DHF were admitted to DPH. Of these, 800 developed DSS: 722 (9%) patients had severe DSS, and 94.5% developed DSS on the fourth day after the initial fever. The average age of the DSS patients was 9.3±3.3; the percentage of newborns (<1 year), children under 5, and children over 5 were 2.4%, 7.3%, and 90.3% respectively. Overall, 52% of the patients were female, 25% were overweight, and 6.4% were malnourished.

A total of 137 patients (17.1%) suffered from respiratory distress. Due to the inability to move the patient from a hospital bed to the Department of Medical Technique, 42 patients underwent an on-bed X-ray. Two of the patients suffered from a breathing disorder, and eventually apnea, and needed an endotracheal intubation to maintain normal breathing. **Table 1** shows more details of these 137 patients.

Factors associated with respiratory distress

The percentage of patients with respiratory distress was higher in younger than in older children, which could be explained by the lower volume of plasma and the stronger permeability in younger patients. The factors shown in Table 2 indicated that the group who suffered from respiratory distress had a greater excretion of urine. Respiratory distress accounted for 31.9% of the severe shock cases but only 15.7% of the shock cases.

Table 2. Sub-clinical and clinical characteristics of pediatric patients with DHF

Characteristics	Mean ± SD	Q1-Q3	N (%)
Breathing disorder			2 (1.5%)
Dyspnea			135 (98.5%)
X-ray			135 (98.5%)
PEI < 15%			21 (50.0%)
PEI 15 – 30%			13 (30.9%)
PEI > 30%			8 (19.1%)
First respiratory distress symptom (hours after parenteral administration)	23.6±10.5	16.5–30.0	
Respiratory distress after 12 hours of treatment			17 (12.4%)
Oxygen therapy			
Number of patients			24 (17.8%)
Hours of treatment	17.1±10.7	7.5–24.0	
NCPAP therapy			
Number of patients			103 (76.3%)
Average PEEP/ NCPAP (cmH_2O)	5.7±1.0		
Hours of treatment	46.1±21.6	30–60	
Ventilator			
Number of patients			8 (5.9%)
Average PIP (cmH_2O)	20±2.1	19–22	
Average PEEP (cmH_2O)	5.9±1.4	5–6	
Hours of treatment	167.8±87.8		
Paracentesis			2 (1.5%)

Abbreviations: DHF: dengue hemorrhagic fever; NCPAP, nasal continuous positive airway pressure, PEI, pleural effusion index, PEEP, Positive End Expiratory Airway, PIP, Peak inspiratory pressure

Table 3. Factors associated with respiratory distress in pediatric dengue shock syndrome patients

Characteristics	No respiratory distress* (n=663)	Respiratory distress* (n=137)	P-value**
Years old	9.55±3.3	7.85±3.3	<0.001
Mucous hemorrhage	10.0 (1.51)	22.0 (16.1)	<0.001
Severe shock	49 (68.1)	23 (31.9)	<0.001

Shock	614 (84.3)	114 (15.7)	<0.001
Hematocrit (%)	48.8±3.9	49.6±4.1	0.02
White blood cell (x1000/mm^3)	4.6±2.4	5.0±2.4	0.07
Platelet (x1000/mm^3)	44.1±24.7	44.1±24.6	0.99
Albumin (g/dl)	38.3±5.4	36.3±5.4	0.003
Lactate (mmol/l)	17.6±7.4	21.9±12.2	<0.001
C-reactive protein >10mg/l	52 (10.0)	16 (14.4)	0.26
Parenteral administration (total)	133.4±13.9	147.9±26.5	<0.001
Parenteral administration (high molecular mass)	46.2±21.9	72.9±32.6	<0.001
Parenteral administration (hours)	26.9±4.3	30.0±6.6	<0.001
Stopped-fluid urine	3.0±1.4	2.0±1.1	<0.001
Re-shock	61 (7.6)	44 (32.1)	<0.001
Use of furosemide after parenteral administration	127 (15.9)	103 (75.2)	<0.001

Data are presented as mean±SD or n (%), **t-test or chi square test

Discussion

DSS is an important medical problem in southern Vietnam, and the annual hospitalization and mortality rates due to severe DHF are relatively high in children. Unlike adults, most children with DHF who are admitted to hospital often develop severe shock. Injury to other organs often takes place in children with prolonged shock, re-shock, or late hospitalization with deep shock, with liver failure, kidney failure, coagulopathy, and respiratory failure being common complications. However, studies on these pediatric issues have been limited.

The medical sectors in Vietnam are mobilizing to meet the population's requirement for healthcare. In recent years, provincial hospitals, including DPH, have opted to treat severe cases of DHF to reduce the burden on central facilities. However, not all local health facilities are adequately prepared in terms of personnel and equipment. Preparing to deal with DHF requires human and financial resources, as well as the training programs, to minimize deaths and sequelae. Mohamed et al. reported that shock occurred in 91.2% of 57 adults with respiratory distress due to DHF.[13]

DPH is a provincial hospital specialized in pediatric medicine and has the ability to treat severe cases of DHF. During the period from January 2015 to June 2017, 800 DSS cases were included in the current study. The mortality rate in the study group was low, when compared to the whole country during the study period. The characteristics of the patients were also common characteristics of children with severe DHF in Vietnam: age over 5 years, high rate of obesity and overweight, and hospitalized due to shock or severe shock. However, 60% of the shock occurs when the child is being monitored at a hospital despite the DHF diagnosis. Therefore, DHF monitoring at the hospital also needs to be tightly chopped down for relatives, families, and health professionals. During the epidemic season, many children are admitted to the hospital, but the medical staff is limited so the monitoring may be poor. According to Yuvarajan et al.,[14] when pulmonary complications are severe, diagnosis and initiation of treatment are often delayed, resulting in increased mortality. Rejuvenating the fluid in a child with pulmonary complications must be done with care because this can increase effusion, increase fluid in alveolar and squamous tissue, and worsen respiratory failure. More research is needed on virus strains, inflammatory substances, prognostic factors, epidemics, myocardial contractility, and treatment measures in children with DHF who have respiratory distress complications. Given the limited resources in Vietnam, we have a large population of patients but not many studies on this issue.

The rate of respiratory failure was 17.1% in the present study. We found that the majority of pediatric patients showed signs of respiratory distress in the form of tachypnea, exertional breathing, and requirement for respiratory support. In total, 1.5% of our patients showed signs of breathing disturbance, with apnea accompanied by cognitive disorders, indicating that the patients should be intubated and ventilated right from the time of infusion to protect against shock. Only 30.1% of the respiratory failure patients had X-rays taken to assess the level of effusion. Half of the patients had low pleural effusion, and 19.8% had high pleural effusion. Other authors have reported rates of 87.4% and 54.2%, respectively,[12] so these rates may differ among treatment units. We do not conduct regular on-bed X-rays because we lack the equipment. We are the unit that treats DHF patients from the beginning, whereas some other units only admit severe cases.

The median onset of respiratory failure was 23.6 hours after the beginning of parenteral administration. Of the affected patients, 12.4% showed signs of early respiratory failure before 12 hours of infusion, and this rate was 48.2% within the first 24 hours of infusion. DHF can cause acute RDS, and the dengue virus antigen was found in alveolar epithelial cells. Increases in the permeability of the alveolar capillary membranes causes alveolar edema and acute RDS. The

increased permeability may be a consequence of increased vascular permeability in patients with DHF.

Wang et al. reported a rate of respiratory failure of 1.8% in 606 dengue-infected adults in China. Factors associated with respiratory failure included age, dyspnea, cough, coagulation disorders, elevated liver enzymes, kidney damage, decreased albumin, and gastrointestinal bleeding.[15] Another study of 52 Indian children with DHF reported a respiratory distress rate of 15.4%, mainly due to pleural effusion, but no cases of acute RDS.[16] In the present study, 17.8% of the patients received respiratory support with oxygen therapy, with an average breathing time of 17.1 hours. The majority of the children (76%) were supported by the NCPAP breathing method, with an average PEEP of 5.7 cmH_2O and an average time of 46.1 hours. CPAP is a suitable treatment measure for patients with DHF, as it helps to improve functional residual capacity and lung and chest elasticity. In the presence of pleural effusion, lung elasticity decreases because the lung parenchyma collapses due to compression.

We installed a ventilator with a low parameter, as described in many other studies and in agreement with the guidelines of the World Society of the Abdominal Compartment Syndrome. In our study, many factors were associated with respiratory distress, including age differences. The average age was lower for the respiratory distress group than for the counterpart group, at 7.85±3.3 and 9.55±3.3 years, respectively. The mucosal hemorrhage characteristics also differed significantly between the groups with and without respiratory distress. The Hct ratio was statistically higher ($p=0.02$) during shock in the respiratory failure group (49.6±4.1) than in the non-failure group (48.8±3.9). The average plasma albumin concentration and the average serum lactate concentration were both higher in the respiratory failure group than in the non-respiratory distress group ($p<0.05$). Puspanjono et al. reported that hyperlactatemia in dengue shock may be considered as a sign of inappropriate shock treatment. They suggest that the serum lactate level can be used as a biochemical sign of tissue hypoxia to assess disease severity.[17] Thanachartwet et al. suggested that serum lactate concentrations ≥2.5 mmol/l are associated with DSS and organ failure, and that lactate levels could be used as a predictor of DSS and/or organ damage.[18] Tatura et al. concluded that plasma albumin concentrations could be used to predict patients with DHF who would likely developed into shock cases.[19] These factors indicate that respiratory failure is related to plasma leakage that is associated with membrane effusion.

Patients were administered a significantly higher total volume of infusion in the respiratory distress group (147.9±26.5 ml/kg) than in the group without respiratory distress (133.4±13.9 ml/kg). Patients were also administered a significantly higher volume of high-molecular-mass infusion in the respiratory distress group (72.9±32.6 ml/kg) than in the group without respiratory distress (46.2±21.9 ml/kg). The use of high-molecular-mass infusions in DHF treatment remains a matter of great controversy, regarding both the types and the use. Theoretically, polymeric solutions have more advantages for increasing capillary permeability in extremely severe cases.

Conclusion

The rate of respiratory failure in children with DF is 17.1% and is mostly at the moderate level and requiring CPAP. Younger age, high plasma loss, re-shock, and the volume of parenteral fluid administration are factors that contribute to respiratory distress in pediatric DHF cases.

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Conflict of interests

The authors had no conflicts of interest to declare in this work.

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