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## CHAPTER 3

# Treatment

### **Loss of plasma volume**

The major pathophysiological abnormality seen in DHF/DSS is an acute increase in vascular permeability leading to loss of plasma from the vascular compartment. Studies reveal a reduction in plasma volume of more than 20% in severe cases. The evidence that supports the existence of plasma leakage includes findings of pleural effusion and ascites by examination or radiography, haemoconcentration, hypoproteinaemia and serous effusion (at post mortem). The fact that no destructive or inflammatory vascular lesions are observed suggests that transient, functional vascular changes due to short-acting mediators occur. Plasma leakage can lead to shock, which, if uncorrected, leads to tissue anoxia, metabolic acidosis and death.

The haemostatic changes in DHF include three elements: vascular changes, thrombocytopenia and disorders of coagulation. All patients demonstrate an increase in capillary fragility, reflected by positive tourniquet tests and easy bruising. Most patients with DSS and some non-shock patients exhibit disseminated intravascular coagulation, as evidenced by concomitant thrombocytopenia, prolonged partial thromboplastin time, a decreased fibrinogen level and increased levels of fibrinogen degradation products. In cases of prolonged uncontrolled shock, disseminated intravascular coagulation can cause bleeding and may play an important role in the development of lethal shock. About one-third of patients who experience shock, mostly those in whom shock is refractory, manifest bleeding, mainly from the gastrointestinal tract. In the majority of patients who die, gastrointestinal haemorrhage is observed.

Early and effective replacement of plasma losses with plasma expander or fluid and electrolyte solution results in a favourable outcome in most cases. With adequate and appropriate fluid administration, DSS is rapidly reversible. Early and rapid resuscitation from shock and the correction of metabolic and electrolytic disturbances will prevent disseminated intravascular coagulation. The prognosis depends mainly on the early recognition and treatment of shock, which depend on careful monitoring and prompt action.

It is not necessary to hospitalize all patients with suspected DHF, since shock develops in only about one-third. The finding of a continuing drop in the platelet count concurrent with a rise in the haematocrit is an important indicator of the onset of shock. So that early signs of shock can be recognized,

patients should have repeated platelet and haematocrit determinations. Parents and other persons caring for patients should be advised to watch for signs of deterioration or warning signs of shock such as restlessness or lethargy, acute abdominal pain, cold extremities, skin congestion or oliguria. The critical period is usually on the day of defervescence, typically after the third day of illness.

### Dengue haemorrhagic fever

Thirst and dehydration result from high fever, anorexia and vomiting; thus fluid intake by mouth should be ample. An electrolyte replacement solution or fruit juice is preferable to plain water. Oral rehydration solution, as for the treatment of diarrhoeal disease, is recommended.<sup>1</sup>

During the acute febrile phase there is some risk of convulsions. Antipyretics may be indicated in patients with hyperpyrexia, particularly those with a history of febrile convulsions. Salicylates should be avoided since they may cause bleeding and acidosis, or precipitate Reye or Reye-like syndrome. Paracetamol is preferable to reduce fever but should be used with caution, in the following doses:

<1 year	60 mg/dose
1–3 years	60–120 mg/dose
3–6 years	120 mg/dose
6–12 years	240 mg/dose.

A dose should be administered when body temperature is greater than 39 °C, but no more than 6 doses should be administered in a 24-hour period.

Patients should be closely observed for signs of shock. The critical period is the transition from the febrile to the afebrile phase of illness, which usually occurs after the third day. Haematocrit determinations are an essential guide to therapy at that stage, since they indirectly indicate the degree of plasma leakage and the corresponding need for intravenous fluid. A rising haematocrit usually precedes changes in blood pressure and pulse. The haematocrit should be determined daily from the third day of illness until the patient's fever has

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<sup>1</sup> If oral rehydration solution is to be given to children under 2 years of age, additional fruit juice or water should be given in the proportion of one volume for every two volumes of oral rehydration solution. Oral rehydration solution consists of the following, dissolved in 1 litre of potable water:

Sodium chloride	3.5 g
Trisodium citrate dihydrate or 2.5 g sodium bicarbonate	2.9 g
Potassium chloride	1.5 g
Glucose	20.0 g

It is important to give oral rehydration solution in small amounts at a steady rate (a teaspoonful every 1–2 minutes).

subsided for 1 or 2 days. If determination of the haematocrit is not possible, haemoglobin determination may be used, although it is less sensitive.

Parenteral fluid therapy can be given in an outpatient rehydration unit for patients in whom fever, vomiting or anorexia produce dehydration. The fluid used to correct dehydration is chosen according to the nature of the fluid loss. In cases of isotonic dehydration, 5% glucose (50g/l) diluted 1:2 or 1:1 in physiological (normal) saline should be used. Bicarbonate-containing solutions should not be used for the initial intravenous management of dehydration in DHF, and should be reserved for cases where there are persistent fluid losses from diarrhoea. The necessary volume of replacement fluid is equivalent to the amount of fluid and electrolyte lost: thus, 10 ml/kg should be administered for each 1% of normal body weight lost. Maintenance fluid requirements, calculated according to the Halliday & Segar formula (Table 3.1), should be added to the replacement fluid volume. Since the rate of plasma leakage is not constant (it is more rapid when body temperature drops) the volume and rate of intravenous fluid therapy should be adjusted according to the volume and rate of plasma loss. Plasma loss can be monitored by changes in the haematocrit, vital signs or volume of urine output. However, even where there is massive plasma loss, judicious fluid replacement is necessary to avoid overhydration.

### ***Example of volume replacement***

A 2-year-old child (normal body weight, 10 kg) has Grade-II DHF with the following indications;

- High fever for 3 days
- Symptoms worsen on day 4 when temperature drops
- Physical examination finds: temperature 37°C, pulse rate 120/minute, blood pressure 100/70 mmHg (13.3/9.3 kPa), petechiae, a positive tourniquet test and the liver enlarged by 2 cm

**Table 3.1**  
Calculations for maintenance intravenous fluid infusion

Body weight (kg)	Maintenance volume (ml) administered over 24 hours
10	100/kg
10–20	1000 + 50 for each kg in excess of 10
>20	1500 + 20 for each kg in excess of 20

Halliday MA, Segar WE. Maintenance need for water in parenteral fluid therapy. *Pediatrics*, 1957, 19: 823. Reproduced by permission of *Pediatrics*.

- Laboratory examination finds: 0–1 platelets/oil-immersion field (100×), haematocrit 45% (baseline 35%).

*Administration of intravenous fluid is necessary as the patient has a >20% increase in haematocrit and early signs of circulatory disturbance (i.e. rapid pulse and worsening condition).*

The following steps should be taken:

- Calculate the intravenous fluid needed, on the assumption of 5% isotonic dehydration:
  - replacement fluid:  $10 \times 50 = 500$  ml
  - daily maintenance fluid:  $10 \times 100 = 1000$  ml
  - total fluid needed:  $500 + 1000 = 1500$  ml/day
- Order 500 ml of 5% glucose (50 g/l) diluted 1:2 or 1:1 in physiological saline (fluid volume should not exceed 500 ml per order, *or* should not be for a period longer than 6 hours; orders should specify type of solution and rate of administration).
- Check vital signs every 1–2 hours and haematocrit every 3–4 hours; monitor urine output and patient's condition.
- Adjust intravenous fluid administration according to vital signs, haematocrit and urine output (see Fig. 3.1).

### ***Indications for hospitalization***

Hospitalization for bolus intravenous fluid therapy may be necessary where significant dehydration (>10% of normal body weight) has occurred and rapid volume expansion is needed. Signs of significant dehydration include:

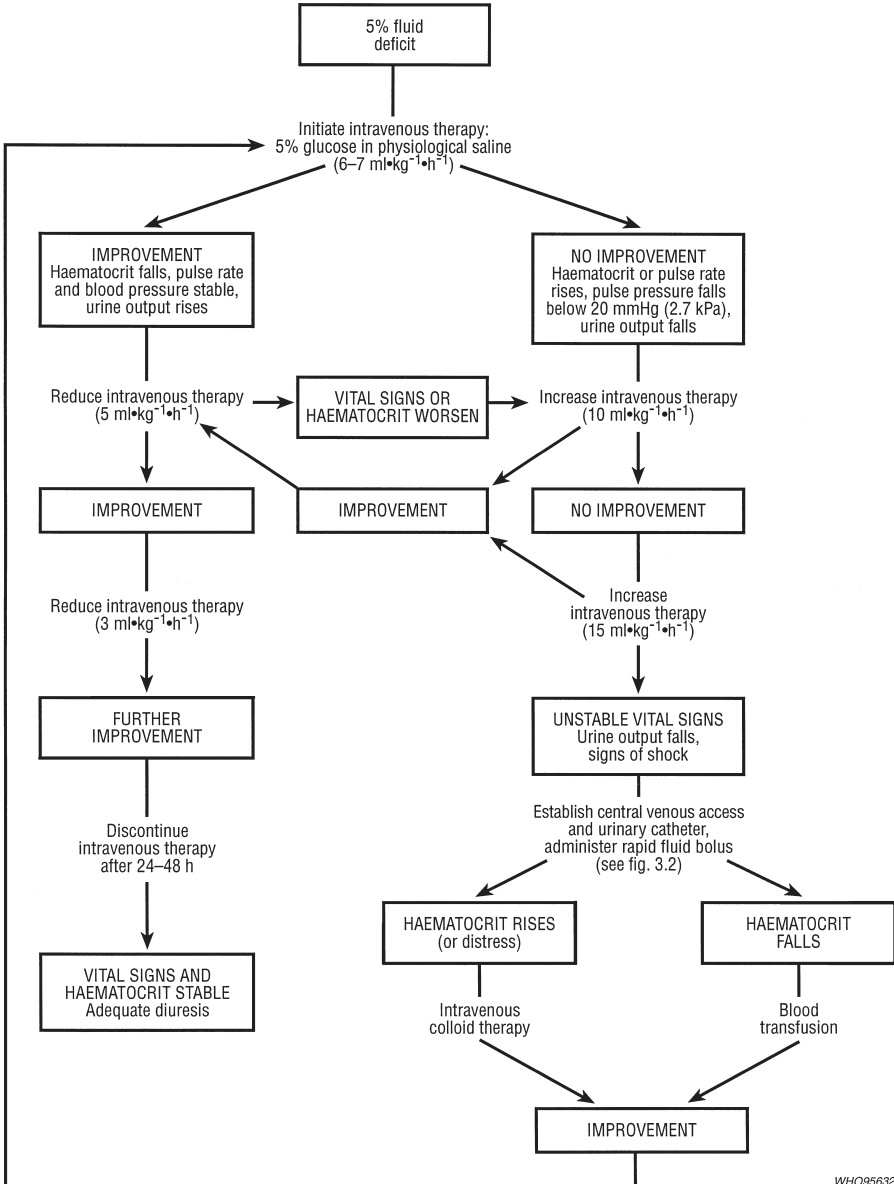
- Tachychardia
- Increased capillary refill time (>2 s)
- Cool, mottled or pale skin
- Diminished peripheral pulses
- Changes in mental status
- Oliguria
- Sudden rise in haematocrit or continuously elevated haematocrit despite administration of fluids
- Narrowing of pulse pressure (<20 mmHg (2.7 kPa))
- Hypotension (a late finding representing uncorrected shock).

### **Dengue shock syndrome**

Shock is a medical emergency. The immediate administration of intravenous fluid to expand plasma volume is essential. Children may go in and come out of shock during a 48-hour period. Consequently close observation round the clock by qualified nursing staff is imperative.

**Fig. 3.1**

Volume replacement flow chart for a patient with DHF and a >20% increase in haematocrit



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### ***Immediate replacement of plasma loss***

Fluids used for rapid volume expansion include the following:

- Physiological saline
- Ringer's lactate or Ringer's acetate
- 5% glucose solution diluted 1:2 or 1:1 in physiological saline
- Plasma, plasma substitutes (e.g. dextran 40) or 5% albumin (50 g/l)

Ringer's lactate, Ringer's acetate or 5% glucose diluted in physiological saline should be administered as a rapid (<20 minutes) intravenous bolus (10–20 ml/kg). Another bolus bringing the fluid dose to 20–30 ml/kg can be administered if necessary. If shock persists, oxygen should be given and the haematocrit should be checked. If the haematocrit is rising, plasma, plasma substitutes or 5% albumin (10–20 ml/kg) should be administered as a rapid bolus, repeated if necessary for a total dose of 20–30 ml/kg of colloidal solution. If shock still persists, haematocrit values should be reviewed for evidence of decline, which may indicate internal bleeding. Fresh whole-blood transfusion (10 ml/kg, if the haematocrit is still above 35%) may be needed in such cases. When shock ceases, the intravenous infusion rate should be reduced and adjusted according to the haematocrit level, urine output and vital signs (see Fig. 3.2).

### ***Continued replacement of further plasma loss***

Plasma loss may continue for 24–48 hours, requiring continued fluid administration. Determination of central venous pressure may be necessary in the management of refractory shock.

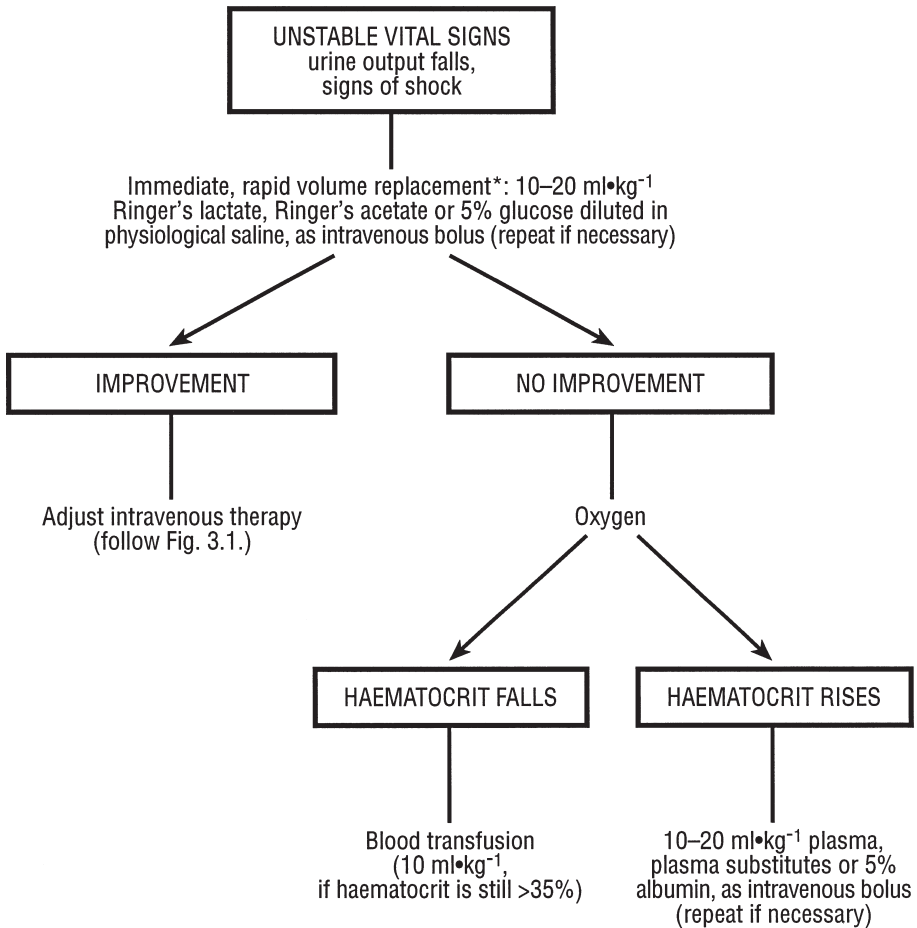
The administration of intravenous fluids should be discontinued when the haematocrit level drops to approximately 40%, with stable vital signs. Good urine flow indicates sufficient circulating fluid. In general, intravenous fluid therapy should not be needed for more than 48 hours after the termination of shock. Reabsorption of extravasated plasma occurs (manifested by a further drop in haematocrit after intravenous fluid has been stopped), and hypervolaemia, pulmonary oedema or heart failure may be caused if more fluid is given. *It is extremely important that a drop in haematocrit at this later stage is not interpreted as a sign of internal haemorrhage.* Strong pulse and blood pressure and adequate diuresis are good signs during this phase. They rule out the likelihood of gastrointestinal haemorrhage, which is found mostly during the shock stage. The return of the patient's appetite is also a sign of recovery.

### ***Correction of electrolyte and metabolic disturbances***

Hyponatraemia and metabolic acidosis can occur in severe cases. Electrolyte levels and partial pressures of blood gases should be determined periodically in severely ill patients and in patients who do not seem to respond as promptly as

**Fig. 3.2**

Volume replacement flow chart for a patient with DSS



\* In cases of acidosis, hyperosmolar or Ringer's lactate solution should not be used.

expected. These indicators will provide an estimate of the magnitude of the electrolyte (sodium) deficit and help determine the presence and degree of acidosis. Acidosis in particular, if uncorrected, may lead to disseminated intravascular coagulation and to a more complicated course. In general, early volume replacement and the early correction of acidosis with sodium bicarbonate result in a favourable outcome.

### ***Sedatives***

Sedative therapy is needed in some cases to restrain an agitated child. Restlessness may be associated with insufficient tissue perfusion, which may require rapid volume replacement, and agitation may also be an early sign of hepatic failure. Hepatotoxic drugs and long-acting sedatives should be avoided. A single dose of chloral hydrate (12.5–50 mg/kg), orally or rectally, is recommended (the total dose not exceeding 1 g).

### ***Oxygen therapy***

Oxygen therapy should be given to all patients in shock, but the nursing staff involved should be aware that an oxygen mask or a tent may increase the anxiety of the patient and should be prepared to manage this eventuality.

### ***Blood transfusion***

Blood grouping and matching should be carried out as a routine precaution for every patient in shock, but blood transfusion is only indicated in cases with significant clinical bleeding. Internal bleeding may be difficult to recognize in the presence of haemoconcentration. A drop in haematocrit, e.g. from 50% to 40%, with no clinical improvement despite adequate fluid administration, indicates a significant internal haemorrhage. Transfusion with fresh whole blood is preferable, and the amount given should be such that the normal red-blood-cell concentration is not exceeded. Fresh frozen plasma or concentrated platelets may be indicated in cases where coagulopathy causes massive bleeding. Disseminated intravascular coagulation is usual in severe shock and may play an important part in the development of massive bleeding or lethal shock. Invasive devices and procedures should be limited to those that are strictly necessary as they may lead to severe bleeding in the presence of coagulopathy. The results of haematological tests (prothrombin time, partial thromboplastin time and thrombin time) should be studied in all patients with shock in order to document the onset and severity of disseminated intravascular coagulation.

### ***Essential laboratory tests***

In assessing a patient's condition, the following tests are recommended:

- Haematocrit
- Serum electrolytes and blood gas studies
- Platelet count, prothrombin time, partial thromboplastin time and thrombin time
- Liver function tests—serum aspartate aminotransferase, serum alanine aminotransferase and serum proteins.

### ***Monitoring patients in shock***

Frequent recording of the vital signs and determination of the haematocrit are important in evaluating the results of treatment. If patients show signs of shock, vigorous therapy should be instituted promptly. Patients should then be under constant and careful observation until there is a reasonable certainty that the danger has passed. The following measures should be taken routinely in such instances:

- Pulse, blood pressure and respiration should be recorded every 30 minutes (or more often) until shock is overcome.
- Haematocrit or haemoglobin levels should be determined every 2 hours for the first 6 hours, then every 4 hours until stable.
- A fluid balance sheet should be kept, recording the type of fluid and the rate and volume of its administration in order to evaluate the adequacy of fluid replacement. The frequency and volume of urine output should also be recorded, and a urinary catheter may be needed in cases of refractory shock.

### **Unusual manifestations of dengue haemorrhagic fever**

The management of DHF patients with acute hepatic failure poses a difficult problem. The early detection of highly elevated levels of serum alanine aminotransferase in patients who exhibit an unusual change in consciousness or abnormal neurological signs (e.g. hyperreflexia) will, if acted upon, have an impact on prognosis and survival. These patients should be given intravenous fluid with extreme caution in order to avoid the excessive fluid replacement that can cause brain oedema and encephalopathy. Colloidal solution should be used early to correct plasma loss. Fluid and electrolyte replacement therapy may prevent mild hepatic coma. In severe cases with a progressive change in consciousness, exchange blood transfusion has been tried and appears to increase survival rate. Most patients with acute liver failure die from severe haemorrhage, renal failure, brain oedema (and sometimes herniation), pulmonary oedema or a superimposed infection.

### **Outpatient and inpatient flow charts**

Outpatient and inpatient flow charts are included in Annexes 3 and 4 to provide guidance on the diagnosis and treatment of DHF/DSS. Physicians may use these charts to become familiar with the decisions involved in providing appropriate medical care to these patients. They may also be useful for training nurses, medical students and paramedical personnel in the identification and treatment of severe cases of dengue virus infection. They are designed for primary and secondary health units where sophisticated electronic monitoring

equipment is not available. If highly technical intensive care is available, judgement must be used to determine the best but least invasive treatment programme for each patient. Additional guidance may be sought from the WHO Collaborating Centre for Case Management of Dengue/DHF/DSS (see Annex 6).

### **Criteria for discharging inpatients**

The following criteria should be met before patients recovering from DHF/DSS are discharged:

- Absence of fever for at least 24 hours without the use of antifever therapy (cryotherapy or antipyretics)
- Return of appetite
- Visible clinical improvement
- Good urine output
- Stable haematocrit
- Passing of at least 2 days after recovery from shock
- No respiratory distress from pleural effusion or ascites
- Platelet count of more than 50 000 per mm<sup>3</sup>.