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Review article

Dengue in Pregnancy-Management Perspectives

Kolitha H. Sellahewa[1], D.K. Upali Marasinghe[2], Mohamed Najimudeen[3].

[1] Associate Professor, Department of Medicine, Melaka-Manipal Medical College, Melaka, Malaysia
[2] Associate Professor, Department of Obstetrics & Gynaecology, Melaka-Manipal Medical College, Melaka, Malaysia
[3] Associate Professor, Department of Obstetrics & Gynaecology, Melaka-Manipal Medical College, Melaka, Malaysia

Corresponding author: Kolitha H Sellahewa, Department of Medicine, Melaka-Manipal Medical College, Jalan Batu Hampar, Bukit Baru, 75150 Melaka, Malaysia; Email: kolithah@gmail.com
Mobile: (6 06) 0183923258
Fax: (6 06) 2817977

Abstract

Dengue in pregnancy is becoming increasingly evident. Pregnancy is associated with severe disease. It is necessary to suspect dengue in acute febrile illnesses in pregnancy as its early diagnosis enables aggressive monitoring to detect plasma leakage early before advent of shock. Appreciating the difference between dengue fever and dengue haemorrhagic fever, accurate identification of the critical phase and fluid therapy appropriate to the phase of illness are of fundamental importance in preventing morbidity and mortality. Normal physiological changes in pulse pressure and haematocrit in pregnancy tend to limit both the diagnostic and therapeutic utility of these critically important data. Judicious fluid therapy, a dynamic approach to fluid infusion and recognition of a fluid quota for the critical phase serves to prevent both shock and fluid overload. Except prior to emergency surgery, prophylactic platelet transfusions for thrombocytopaenia have limited place. Premature birth, fetal malformations, neonatal thrombocytopaenia and post-partum haemorrhage are specific fetal and maternal complications.

Key words: dengue, pregnancy, management

Introduction

Dengue which was initially prevalent in the tropical countries is now a global problem. It is endemic in more than 100 countries. The threat of dengue outbreaks exist in Europe. In 2010 Local transmission was reported in France and Croatia, and imported cases have been detected in three other European countries. In 2012 an outbreak of over 1800 cases was reported in Madeira Islands Portugal. WHO estimates that 2.5 billion

populations are at risk of dengue. 50-100 million people are estimated to be infected with dengue worldwide every year. 500,000 people are estimated to develop severe disease requiring hospitalization.[1]

With 280 million pregnancies every year dengue in pregnancy is increasingly evident.[2] The kinetics of plasma leakage in DHF is such that properly timed judicial fluid therapy is critical in preventing morbidity and mortality in dengue haemorrhagic fever (DHF). Management of dengue in pregnancy should not be the prerogative of physicians who are often consulted too late in the disease process. Unlike other febrile illnesses in pregnancy, dengue requires timely interventions to prevent mortality. It is thus essential for obstetricians to take the lead role. To do so all medical personnel caring for pregnant women should be able to diagnose dengue infection early, recognise the difference between dengue fever (DF) and DHF, and be thoroughly conversant with the basics of fluid therapy. A clear understanding of the disease course, pathogenesis, and attended pathophysiological changes in DHF are an essential pre-requisite to meet this goal.

Disease spectrum and pathogenesis

Infection by any one of the four serotypes of dengue virus (DENV) remains asymptomatic in the vast majority. Clinical spectrum among those with symptomatic infection ranges from undifferentiated fever (viral syndrome), DF, and DHF to the expanded dengue syndrome with isolated organopathy (unusual manifestations). DF can be without haemorrhage or have unusual haemorrhage, while DHF can be without shock or with shock i.e. dengue shock syndrome.[3] The WHO criteria for the clinical diagnosis of DHF requires the presence of acute and continuous fever of 2 to 7 days, haemorrhagic manifestations associated with thrombocytopenia (100,000 cells/c.mm or less) and haemoconcentration (haematocrit >20% from baseline of patient or population of same age). Haemorrhagic manifestations could be mucosal and or skin, or even a positive tourniquet test which is the commonest. Hepatomegaly occurs at some stage of DHF and often precedes plasma leakage and hence a valuable early predictor of plasma leakage.[3, 4]
DHF is most common in secondary dengue infection. Abnormal haemostasis and plasma leakage are the main pathophysiological hall marks in DHF. DHF patients have a stereotyped course of febrile, critical and convalescent phases. Febrile phase lasts 2-7 days. Critical phase begins with defervescence after 3-6 days into the disease course, and lasts for 48 hours. Critical phase is characterised by plasma leakage. Convalescence follows the critical phase after cessation of plasma leakage and usually lasts 5-14 days.[5, 6]

Plasma leakage in DHF

Plasma leakage is peculiar only to DHF and not DF.[7,8,9]. It lasts only 48 hours. Plasma leakage is specific to the pleural and peritoneal surfaces .In DHF there is no vasculitis and hence no injury to the vessel walls, and plasma leakage results from cytokine mediated increase in vascular permeability. The ensuing movement of albumin and the resultant reduction of intravascular oncotic pressure facilitate further loss of fluid from the intravascular compartment. The basic Starling principle still holds true in explaining microvascular ultrafiltration based on the balance of the oncotic and hydrostatic pressures. The gradual onset of plasma leakage and intravascular volume depletion allows physiological compensation. Thus, baroreceptor mediated reflexes to volume depletion result in tachycardia, increase in diastolic blood pressure and narrowing of pulse pressure. These physiological parameters are of critical importance in the early detection of plasma leakage and guidance to fluid therapy. [10, 11, 12, 13]

Haemorrhagic manifestations in DHF

The pathogenesis of bleeding in DHF is unclear even though well recognised coagulation disturbances do exist. The clinical haemorrhagic manifestations range from a mere positive tourniquet test, skin petechiae and ecchymoses to epistaxis, and gum bleeding to severe gastrointestinal haemorrhages. Thrombocytopaenia is a consistent finding, while prolonged partial thromboplastin time and reduced fibrinogen concentration are the other abnormal haemostatic indices evident from early in the disease course. These haematological abnormalities seem to correlate better with the timing and severity of plasma leakage rather than the clinical haemorrhagic manifestations.[14]
Thrombocytopaenia is initially due to bone marrow suppression during the febrile viraemic phase of the illness. Progressive thrombocytopaenia with defervescence result from immune mediated platelet destruction. Virus-antibody complexes have been detected on the platelet surface of DHF patients suggesting a role for immune-

mediated destruction of platelets.[15] Augmented platelet adhesiveness to vascular endothelial cells resulting from the release of high levels of platelet-activating factor by monocytes with heterologous secondary infection also contributes to the thrombocytopaenia.[16] Thrombocytopaenia however correlates poorly with bleeding manifestations. Spontaneous bleeding is uncommon even with counts below 100, 000 cells/c.mm. It is strongly associated with the severity of vascular leakage. Counts below 100, 000 cells/c.mm or a rapid drop in the platelet count is associated with severe disease.[17, 18] Low plasma fibrinogen and prolonged APTT in the absence of shock early in the disease is to be expected in DHF and interpreted as heralding plasma leakage and not DIC, and its magnitude gives an idea of the severity of leakage. On the contrary the same indices of coagulopathy should have a different interpretation in the setting of shock owing to the confounding effects of hypovolumia and hypoxia and the probability of associated DIC in such a setting.[19]
Similarly thrombocytopaenia is best used as a marker of severe disease particularly when it is < 100,000 cells/c.mm or when there is a rapid drop. It is more useful as an indicator of prognosis during the disease course rather than a parameter for therapeutic interventions. Recognising the poor correlation of thrombocytopaenia with bleeding should caution the clinician against the futility, albeit danger of prophylactic platelet transfusions.[20]

Maternal complications

Dengue infection in pregnancy carries the risk of miscarriage, premature birth, abruption and post-partum haemorrhage. In addition, there is an increased risk of maternal death from DIC and acute renal failure. The potential risk of haemorrhage secondary to thrombocytopenia impact management options and obstetric decisions, particularly the mode of delivery. Although the liver is not a primary target of dengue, hepatic involvement ranging from elevated transaminase levels to acute fulminant hepatitis has been detected.[21, 22, 23, 24]
Pre-eclampsia has been reported previously in intra partum dengue fever. Eclampsia in a pregnant patient with dengue is a rare occurrence. Tagore S, Yam CF Kwek reported a case in the Singapore Med J 2007, regarding development of seizures within 24hours post-partum with hyper-reflexia and raised urinary protein and evidence of focal ischaemic areas in the brain. Pregnant women with dengue may be diagnosed with other febrile illness or HELLP syndrome, especially if they present with elevated liver enzymes and low platelet counts[25]

Fetal - neonatal complications

The pathogenesis of neonatal effects of maternal dengue infection is poorly understood. Maternal-foetal transfer of dengue-specific IgG is implicated in the pathogenesis of neonatal DHF.[24] Fever, petechial rash, thrombocytopenia, leukopenia, elevated liver enzymes, hepatomegaly, pleural effusion, premature birth; foetal malformations, miscarriages, and low birth weight have been reported. Miscarriage and still birth is associated with dengue when the illness is severe. Dengue can also be transmitted directly from ill mother through placenta to the fetus in later pregnancy with variable effects to the fetus.[26] An increase in the incidence of fetal neural tube malformation in women who had dengue in the first quarter of pregnancy has been reported,[27,,28] but such an association has been demonstrated following other febrile illnesses as well raising the possibility of pyrexia causing the neural tube malformation rather than a teratogenic effect of the virus *per se*.[28]
There is no convincing evidence to suggest that dengue fever of any sort causes congenital abnormalities of the fetus[29].
Risks to the foetus include intrauterine growth retardation and coagulation disturbances in late pregnancy, increased risk of foetal haemorrhage, and foetal death. Vertical transmission is associated with neonatal thrombocytopenia that necessitates platelet transfusions.[30,31,32,33]

Management concerns in pregnancy

Key areas of management concerns imposed by pregnancy are in the early diagnosis of DHF, differentiation from HELLP syndrome, detection of clinically in apparent internal haemorrhage, optimisation of fluid therapy and obstetric decisions on delivery options.
Narrow pulse pressure (< 25 mm Hg) and tachycardia are critical in detecting plasma leakage. Its usefulness in DHF complicating pregnancy is a matter of concern owing to the physiological tachycardia and widening of pulse pressure during the first two trimesters of pregnancy reaching nadir by approximately 28 weeks of gestation.[34] its utility for diagnosis of plasma leakage and fluid therapy must be interpreted within this context.

Plasma leakage and attendant haemoconcentration result in a rise in haematocrit. Changes in the haematocrit are utilised not only for the early diagnosis of plasma leakage but also in the detection of internal haemorrhage and subtle adjustments to fluid therapy. Below normal haematocrit in pregnancy tends to confound the diagnostic and therapeutic utility of this vital investigation. The dynamics of pulse pressure and haematocrit must therefore be intelligently correlated with accurate baseline pulse pressure and haematocrit in detecting both plasma leakage and internal haemorrhage, as well as improving the appropriateness and accuracy of fluid therapy for both shock and fluid overload. It is thus essential to accurately record the pulse rate, blood pressure, pulse pressure, and FBC preferably on the first day of illness.

Elevated liver enzymes and low platelet counts commonly encountered in dengue may create confusion with the diagnosis of haemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, which occur in women with pre-eclampsia and eclampsia. Evidence of haemolysis and positive serology or viral PCR may facilitate the differentiation.[35,36]

Pregnancy is associated with severe disease. Certain co morbid states like diabetes, asthma, hypertension and ischaemic heart disease also tend to give rise to severe disease. Anticipation of severe disease warrants more aggressive monitoring of all pregnant women with suspected dengue infection irrespective of the condition at the time of presentation and diagnosis and even in the absence of co-morbid states.[3, 20]

Risk of bleeding is greatest in the critical phase. Surgery and induction of labour or any other intervention that could provoke labour should be avoided as far as possible during this critical phase of 48 hours.[20]

Management pre-requisite

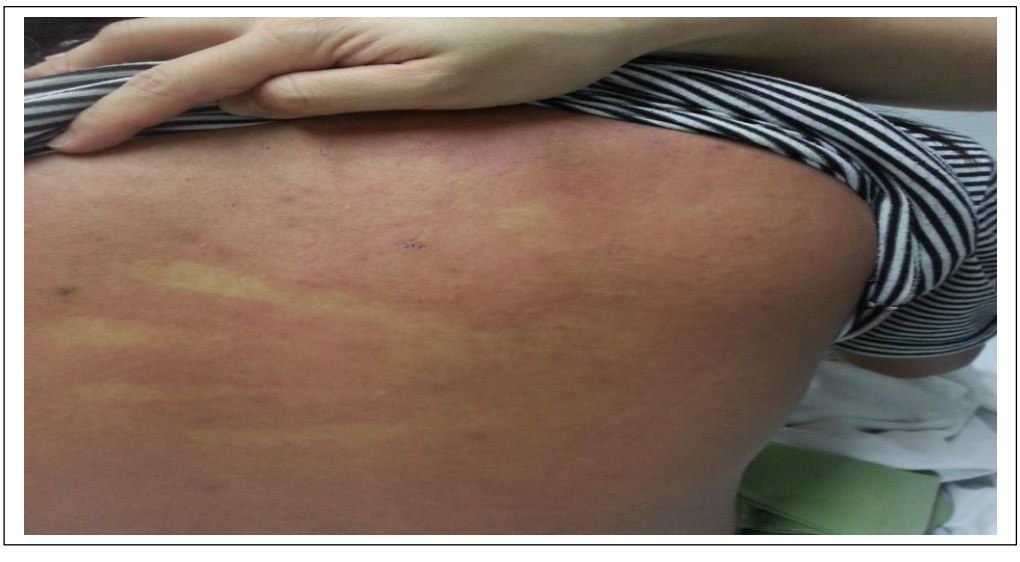
Proper management of dengue requires one to diagnose dengue infection early preferably within the first 3 days of the onset of fever. The next step requires identification of the clinical type as DF or DHF. These are two distinct clinical entities with different management approaches and outcomes. There is no plasma leakage in DF and consequently has an excellent prognosis. DHF on the other hand is characterized by plasma leakage and goes through a highly stereotyped course comprising; febrile, critical and convalescent phases. Clinicians need to be alert and vigilant to identify DHF patients early at the inception of plasma leakage before shock sets in. Judicious fluid therapy appropriate to the stage of the illness could offset adverse events and ensure a smooth convalescence and favourable outcome.

Management strategy

Early diagnosis

Early diagnosis requires one to be vigilant of dengue in all pregnant women with an acute febrile illness particularly in dengue endemic areas and among those who had travelled to such areas. Arthralgia, myalgia and diffuse blanching erythema are useful clinical features for early diagnosis. Complete blood count should be done from day 2 onwards. The presence of leucopoenia and thrombocytopaenia in this clinical setting should suffice to manage as dengue.

Diffuse blanching erythema



Differentiate between DF and DHF

In DF there is no plasma leakage while in DHF there is plasma leakage which should be suspected by the presence of tachycardia when afebrile, pulse pressure is equal to or < 25 mm Hg, capillary refill time is > 2 seconds and a rise in the HCT. This should be confirmed by ultrasonography to detect pleural effusions and ascites quickly and non-invasively before these are clinically overt. Non fasting serum cholesterol < 100 mg/dl and Serum albumin <3.5g/dl are additional investigations resorted to detect plasma leakage early if in doubt.
Once DHF is confirmed by detecting evidence of plasma leakage it is essential to determine the time of entry into the critical phase and its predicted end. It is computed by analysing all the parameters of the full blood counts done during the febrile phase arranged in chronological order. The time at which the total WBC is at a low nadir, differential count shows a change from lymphocyte predominance to polymorphonuclear dominance, HCT has increased and platelet count is < 100,000c.mm is usually taken as the point of entry into the critical phase. 48 hours is projected from that point to predict the end of the critical phase. This information as well as the ideal body weight of the patient is vital for rational and precise fluid therapy. Blind and empirical fluid therapy is no longer advocated. Fluid therapy has to be precise and should not be embarked on until all the basic information is accurately determined and documented.
Throughout the entire course of the illness the practitioner has to be acutely aware of the stage of the illness, and if in the critical phase, the precise point in the time scale. Accurate monitoring of the clinical status, vital signs, and hourly urine output and its accurate documentation in the specific charts appropriate to the phase of the illness form an integral part of management.

Fluid therapy

Fluid therapy is the cornerstone of management of DHF. Its quantity, quality and route of administration are determined by the phase of illness and the status of the monitoring parameters. Unattended plasma leakage inevitably leads to hypotension and shock owing to intravascular volume depletion. The objective of fluid therapy is to offset this tendency by judicious fluid therapy aimed at matching the plasma leakage and thereby preventing intravascular volume depletion.

Febrile phase:

In the majority, oral fluid is sufficient. IV fluid is not mandatory and should be considered only if oral feeding is hampered by severe vomiting. Prescribe only the maintenance quantity (2 – 2.5L/24 hrs.) Additional fluid will be needed to compensate for vomiting and diarrhoea when present. Water alone is insufficient, electrolytes too are essential. Oral rehydration fluid, fruit juices and soups are good options. However avoid black and red coloured drinks.

Critical phase:

Administer only the calculated fluid quota of ***M+5%***, which is the total quantity for the ***entire 48 hour period of the critical phase***. This includes the total of ***both oral and IV*** fluids.[3,20] Do not give fluids at a flat rate; it should be adjusted hour by hour to match the dynamics of fluid leakage. Most will require only crystalloids for the entire phase of plasma leakage. Few patients will need colloids (Dextran40 and 6% starch solution) as well. Isotonic saline is a good crystalloid to start with initially at the rate of 1.5ml/kg. body weight /h. Infusion rate should be progressively increased every 4-6h to 3 ml/kg. body weight /h and then 5 ml/kg /h around 24 hours into the critical phase when plasma leakage is maximal (7ml/kg/hr.) after which it should be gradually decreased. It should always be kept in mind that there is no hard and fast rule to fluid therapy, it has to be flexible, and sometimes needs to be adjusted hour by hour based on the dynamics of the monitoring parameters and individual requirements of the patient.

When the desired goal of adequate ***hourly urine output of 0.5ml -1ml/kg*** and satisfactory ***pulse pressure of > 25 mm Hg*** cannot be maintained, and there is a need to frequently increase the crystalloid infusion rate, rapid plasma leakage should be suspected and a colloid in the form of Dextran 40 should be substituted for saline without delay. Dextran 40 causes volume expansion and remains in the circulation for approximately 4 hours and impacts a more sustained improvement in the haemodynamic status. Colloids should also be considered if

the calculated fluid quota is approaching exhaustion while still early in the critical phase. Colloids enable one to restrict and conserve the fluid quota while maintaining the desired haemodynamic stability which otherwise would have required a larger volume of crystalloid. Under these circumstances Dextran40 Is the preferred colloid around the peak of plasma leakage but 6% starch would be a better choice towards the end of plasma leakage. Colloids should be given as boluses and not infusions. Capillary haematocrit should be checked before and 15 minutes after each fluid bolus. Haematocrit drops by 10 points after a Dextran bolus. Haematocrit should be checked as frequently as is deemed necessary throughout the critical phase to base interventional decisions along with the relevant data from the monitored vital signs.
Accurate identification of the time of entry into the critical phase, precise calculation of the fluid quota based on the ***ideal body weight or actual body weight whichever is lighter (maximum 50kg and use the weight prior to pregnancy)*** for the entire period of 48 hours of plasma leakage, and subtle intelligent manipulations between isotonic saline, Dextran 40 and 6% starch enable one to work with in the fluid quota and thereby prevent both shock as well as fluid overload.

Calculation of fluid quota

M = 100ml/kg for first 10 kg

+ 50 ml/kg for next 10 kg

+ 20 ml/kg for balance weight

5% of body weight = 50 ml x ideal body weight

Maximum body weight taken for calculations is **50 kg**

4600 ml of fluid is the maximum

Monitoring

Clinical status

Vital signs:

- Heart rate
- BP & Pulse pressure
- CRFT

Hourly UOP

HCT – priority during critical phase

Convalescent phase

A wide pulse pressure and an hourly urine output in excess of 1ml/kg body weight herald the onset of the convalescent phase. Fluid requirement is only the maintenance quantity which should be given orally. IV fluids are not mandatory and could even be harmful. Leaked out fluid gets reabsorbed during this phase, hence, colloids particularly Dextran 40 should not be given in this phase of the illness which by volume expansion can precipitate pulmonary oedema.

Symptomatic therapy

Paracetomol is the only antipyretic agent that should be used to control fever, myalgia and headache. NSAIDs of any form including Diclofenac suppositories and Mefenamic acid should not be used for any patient with suspected dengue to control the fever. Antibiotics also should not be used at any stage of the disease unless there is a bacterial co-infection.

Adjuvant therapy

1. Antibiotics should be given only if there is co-infection with a bacterial pathogen.
2. Platelet transfusions: There is no place for prophylactic platelet transfusions even with platelet counts as low as 10,000/ c.mm. It is indicated for significant bleeding i.e.>10ml/kg body weight in association with a platelet count of <10,000/c.mm, DIC, and in patients with intracranial haemorrhages. Platelet transfusions should be given prophylactically prior to emergency caesarean section or any other urgent surgery.[20]
3. Fresh frozen plasma: Prophylactic transfusions are not recommended.
4. Steroids and intravenous immunoglobulins are not recommended in the light of currently available evidence.[20]
5. Factor VII: It is used only to buy time to arrest bleeding when a specific and definitive intervention is planned to treat the root cause of bleeding .e.g. band ligation of oesophageal varices.
6. Tranexamic acid: This is given at a dose of 1gram 8 hourly when there is bleeding per vagina.

Management of complications

Accurate and aggressive management appropriate to each phase of the illness can prevent complications. It is thus essential to be aware of the precise phase of the illness when managing DHF to ensure a smooth convalescence and predictable recovery. Prolonged shock and the attended chronic hypoxemia trigger the cascading life threatening complications ranging from hepatic failure and acute renal failure to severe bleeding and DIC.
Fluid overload is the other major complication which by respiratory compromise aggravates hypoxemia and its attendant adverse consequences.

Shock:

It should be prevented by good monitoring of vital signs and evaluation of all the haematological parameters of full blood counts in the febrile phase to detect early entry into the critical phase and then by frequent monitoring and judicious fluid therapy in the critical phase.
Shock with a narrow pulse pressure and hypotension is treated initially with a crystalloid (isotonic Saline) bolus of 10 ml/kg body weight over 1 hour to open up the microvasculature. If there is no haemodynamic improvement a second crystalloid bolus is infused. A Colloid bolus is given at a dose of 10ml/kg body weight over 1 hour if there is no improvement after 2 crystalloid boluses. If the haematocrit drops by more than the expected value after these interventions, and the patient remains unstable clinically in apparent internal haemorrhage (usually to the gastrointestinal tract) should be suspected and packed red cells (PRC) transfused early. Volume of PRC to be transfused should be computed on the basis that 5ml/kg of PRC will raise the HCT by 5%.
Profound shock (unrecordable blood pressure) is treated in the same way except that the initial crystalloid bolus is given faster over 15 minutes.[20]
In all patients with shock HCT should be checked before and after each fluid bolus and venous blood samples must be collected to check for acidosis, hypocalcaemia, hypoglycaemia and electrolyte disturbances. Acidosis should be corrected with IV sodium bicarbonate if the pH is <7.35 and HCO3 is <15 mmol/l. Early correction of acidosis can annul the tendency for severe bleeding and DIC in patients with dengue shock; hence, if facilities for blood gas analysis are not available 50 ml of 8.4% sodium bicarbonate diluted in 50 ml of saline can be given IV empirically. The adverse impact of acidosis in DHF dictates the selection of a higher cut off point (pH is <7.35 and HCO3 is <15 mmol/l) for using sodium bicarbonate unlike in the correction of metabolic acidosis in other conditions. Similarly 10 ml of 10% calcium gluconate IV over 10 minutes can be given empirically as these patients are invariably hypocalcaemic, which contributes to haemodynamic instability.

Fluid overload:

This is usually encountered in the convalescent phase and is treated aggressively with repeated doses of IV furosemide at 1mg/kg body weight. For fluid overloaded patients who are haemodynamically unstable furosemide should be given mid-way of a colloid infusion or blood transfusion.[3, 20]

Conclusion

Dengue infection should be suspected in any pregnant woman with an acute febrile illness particularly in endemic areas and those returning from endemic countries. Increased propensity to severe disease in pregnancy necessitates greater vigilance to detect DHF early. Judicious fluid therapy appropriate to the phase of illness can prevent morbidity and mortality. Computation of the critical phase and calculation of a fluid quota based on ideal body weight and a dynamic approach to fluid therapy can reduce morbidity and mortality. Appropriate use of full blood counts, capillary haematocrit and ultrasonography will improve the accuracy of interventional decisions and impact favourable outcomes.

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