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Promethazine hydrochloride injection

Boxed warning added

Canada. Health Canada informed healthcare professionals and the public of changes to the prescribing information, including the addition of a boxed warning, for promethazine hydrochloride injection. Injectable promethazine is an antihistamine drug that is used to treat a wide range of conditions, including certain types of allergic reactions, motion sickness, nausea, vomiting and as a sedative. The warning includes the following safety information:

- Promethazine is not to be used in children under the age of two years due to the potentially fatal risk of respiratory depression.
- Caution should be used when administering promethazine in children aged two and up: healthcare professionals are recommended to use the lowest effective dose, and the use of other drugs that may also slow breathing should be avoided.
- Promethazine is not to be injected subcutaneously due to the risk of serious tissue injury.
- The preferred route of administration for promethazine is deep intramuscular injection. Other routes of injection, particularly on to arteries or veins, have been associated with serious tissue injury.
- Regardless of where on the body the drug is injected, promethazine has the potential to occasionally cause chemical irritation and in rare cases severe tissue damage at the site of injection, including cases of gangrene. Patients should immediately report any persistent or worsening pain or burning sensation they feel at the site of injection.

(See WHO Pharmaceuticals Newsletters No. 6, 2009 & No. 1, 2010 and No. 5, 2009 for warnings on the risk of severe tissue injury in New Zealand and the USA, respectively).

Reference:

Advisories, Warnings and Recalls, Health Canada. 26 April 2010 (www.hc-sc.gc.ca).

Cover picture

CARL WILHELM SCHEELE (1742-1786)

Greatest of pharmacist-chemists, Scheele experimented constantly in Swedish apothecary shops, gave the world many chemical discoveries, including oxygen, chlorine, fruit acids, and glycerin, that contribute to today's industry and daily life.

One of a series: *A History of Pharmacy in Pictures*, presented by Parke, Davis & Company.

George A. Bender, Director © 1954 Robert A. Thom, Artist

Prescribing in liver disease

Summary

As the liver is responsible for the metabolism of many compounds, knowledge of a patient's hepatic function is required for the safe prescribing of many drugs. Assessing liver function by way of a patient history, examination and blood tests such as serum albumin and bilirubin, as well as prothrombin time, is recommended before prescribing some medications. Liver enzyme concentrations may be useful indicators of hepatocellular damage or enzyme induction. For drugs dependent on hepatic elimination, careful choice of compounds and their dose is prudent if liver function is significantly compromised. Drug interactions must also be considered if a common metabolic pathway exists.

Key words: drug prescribing, hepatic metabolism.

(Aust Prescr 2009;32:32-5)

Introduction

The metabolism of many drugs depends on adequate hepatic function. Drugs with a narrow therapeutic range (that is, with little difference between toxic and therapeutic doses) run the risk of accumulating and causing toxicity in patients with hepatic disease.

The liver receives a dual blood supply with about 20% of blood coming from the hepatic artery and 80% from the portal circulation. The blood flow to the liver is around 20-25% of the total cardiac output. Toxins, infectious agents, medications and serum inflammatory mediators may result in a diverse range of disease processes leading to loss of normal histological architecture, reduced cell mass and loss of blood flow. Consequently, functional liver capacity may be lost.

Assessing hepatic function is necessary so that appropriate adjustment of drug dose can be made. However, this is not always straightforward as there is no single test that reliably measures liver function.

Drug metabolism in the liver

The liver is the principal organ of metabolism in the body although other sites are involved such as the gut wall, kidney, skin and lungs. Drug metabolism, by means of enzyme reactions in the liver, is the body's main method of deactivating drugs. Drug molecules are converted into more polar compounds, which aids their elimination. Generally, metabolism results in the loss of pharmacological activity because transport to the site of action is limited due to reduced lipid solubility, or because the molecule is no longer able to attach to its receptor site. However, in some circumstances drugs are metabolised to more active forms, for example the conversion of codeine to morphine, primidone to phenobarbitone and amitriptyline to nortriptyline.

Concentrations of enzymes involved in both phase I and II reactions vary significantly between individuals with normal hepatic function and even more so between the healthy population and those with hepatic impairment.

Phase I reactions

Most drugs are lipophilic and therefore readily cross the cell membrane of the enterocyte. In the process of liver metabolism these substances are converted into more hydrophilic compounds. Hydrolysis, oxidation and reduction are the three types of phase I reactions that do this in the liver. These mainly involve a subset of mono-oxygenase enzymes called the cytochrome P450 system. The most common reaction is hydrolysis which involves the addition of a molecular oxygen atom to form a hydroxyl group, with the other oxygen atom being converted to water (for example, the conversion of aspirin to salicylic acid). Other types of phase I reactions include oxidation via soluble enzymes such as alcohol dehydrogenase, and reduction (for example nitrazepam).

Phase II reactions

These reactions involve conjugation which is the attachment of molecules naturally present in the body to a suitable link in the drug molecule. Most compounds will have undergone a phase I reaction (for example, addition of a hydroxyl group) before the conjugation step can occur.The main conjugation reaction involves glucuronidation (for example with morphine), but other conjugation mechanisms include acetylation (sulfonamides) or the addition of glycine (nicotinic acid) and sulfate (morphine). Natural substances such as bilirubin and thyroxine may be metabolised by the same pathways. The resulting conjugate molecule is usually

pharmacologically inactive and substantially less lipophilic than its precursor so it is more readily excreted in the bile or urine.

In some circumstances the parent compound is a prodrug so the metabolite is active (for example, codeine is converted to morphine). A common cause of capacity limited hepatic metabolism is the amount of the conjugate available. Paracetamol overdose is an example of this situation. With normal prescribed doses of paracetamol, the toxic metabolite (N-acetyl-p-benzoquinone imine or NAPQI) is efficiently detoxified by conjugation with glutathione as a phase II reaction. However, when a large amount of NAPQI is generated, the total quantity of available glutathione may be consumed and the detoxifying process becomes overwhelmed. Phenytoin and warfarin are other drugs where capacity limited hepatic metabolism can occur.

Excretion

Following metabolism, compounds are then either excreted directly into the bile, or re-enter the systemic circulation and are excreted as polar metabolites or conjugates by the kidney.

If excreted in the bile (mainly glucuronidated drugs), the compound enters the biliary duct system and is secreted into the upper small intestine. Then throughout the ileum, these conjugated bile salts (some of which have drugs attached to them) are reabsorbed and transported back to the liver via the portal circulation. This is known as enterohepatic circulation. Each bile salt is reused approximately 20 times and often repeatedly in the same digestive phase. The implications of this process are that compounds may reach high hepatic concentrations resulting in significant hepatotoxicity. Some drugs that undergo enterohepatic cycling to a significant extent include colchicine, phenytoin, leflunomide and tetracycline antibiotics.

Systemic drug availability

After drugs are absorbed from the gut, a proportion of the dose may be eliminated by the liver before reaching the systemic circulation. This pre-systemic or first pass elimination is determined by the hepatic clearance or extraction for the compound. Hepatic clearance depends on three factors:

- extent of drug binding to blood components such as albumin
- blood flow to active metabolic cells, which is dependent on the architecture in the liver
- functional hepatocytes.

The hepatic extraction ratio of a drug will indicate if its elimination is dependent on blood flow and hepatocyte function (highly extracted) or hepatocyte function alone (poorly extracted). Some examples of high and low extraction drugs are listed in Table 1.

Table 1

Some examples of drugs with high and low hepatic extraction

High extraction ratio	Low extraction ratio
Antidepressants	Non-steroidal anti-inflammatory drugs
Chlorpromazine/haloperidol	
Calcium channel blockers	Diazepam
Morphine	Carbamazepine
Glyceryl trinitrates	Phenytoin
Levodopa	Warfarin
Propranolol	

Hepatic conditions

Chronic liver disease is more predictably associated with impaired metabolism of drugs than acute liver dysfunction.

However, in cases of severe acute liver failure, the capacity to metabolise the drug may be significantly impaired.

In the chronic state, cirrhosis of any aetiology, viral hepatitis and hepatoma can decrease drug metabolism. In moderate to severe liver dysfunction, rates of drug metabolism may be reduced by as much as 50%. The mechanism is thought to be due to spatial separation of blood from the hepatocyte by fibrosis along the hepatic sinusoids.

The use of certain drugs in patients with cirrhosis occasionally increases the risk of hepatic decompensation. An example of this is the increased risk of hepatic encephalopathy in some patients who receive pegylated interferon alfa-2a in combination with ribavirin for the treatment of chronic active hepatitis related to the hepatitis C virus. In addition, co-infection with hepatitis B or C virus, even in the absence of cirrhosis, increases the risk of hepatotoxicity from

antiretroviral therapy in patients with coexistent HIV infection.

In the presence of chronic liver disease, there is potential for changing the systemic availability of high extraction drugs, thereby affecting plasma concentrations. A potential consequence of liver disease is the development of portosystemic shunts that may carry a drug absorbed from the gut through the mesenteric veins directly into the systemic circulation. As such, oral treatment with high hepatic clearance drugs such as morphine or propranolol can lead to high plasma concentrations and an increased risk of adverse effects.

Liver damage can also affect drugs with low hepatic clearance. For instance, the effect of warfarin, which has a low extraction ratio, is increased due to the reduced production of vitamin K-dependent clotting factors.

The pharmacokinetic interaction between alcohol and drugs is more complex. An acute ingestion of alcohol may inhibit a drug's metabolism by competing with the drug for the same set of metabolising enzymes. Conversely, hepatic enzyme induction may occur with chronic excessive alcohol ingestion via CYP2E1 resulting in increased clearance of certain drugs (for example phenytoin, benzodiazepines). After these enzymes have been induced, they remain so in the absence of alcohol for several weeks after cessation of drinking. In addition, some enzymes induced by chronic alcohol consumption transform some drugs (for example paracetamol) into toxic compounds that can damage the liver.

In the presence of cholestatic jaundice, drugs and their active metabolites that are dependent on biliary excretion for clearance will have impaired elimination. Further impairment will occur if the compound is excreted as a glucuronide and is subject to enterohepatic circulation.

Evaluating hepatic function

A clear patient history with respect to alcohol, illicit drug use and toxic industrial exposure must be recorded. The medication list including supplements such as iron, vitamin A and herbal remedies is vital. A family history of diseases such as alpha-1 antitrypsin deficiency, iron storage diseases, porphyries and diabetes mellitus may alert the physician to the potential for liver impairment.

It is also important to look for signs of acute or chronic liver disease such as the presence of jaundice, spider naevi, palmar erythema, ascites, abdominal distention, hepatomegaly, splenomegaly and caput medusa. If there is clinical evidence of liver disease, further investigation is required. This includes liver function tests and an ultrasound of the abdomen. A portal vein Doppler study is also recommended to assess for the presence of portal hypertension. A slowing or reversal of portal vein blood flow indicates portal hypertension which may be related to either liver cirrhosis or portal vein thrombosis.

In renal disease, serum creatinine concentration and the glomerular filtration rate provide a reasonable guide to drug dosage requirements. In contrast, there is no single test that measures liver function so a reliable prediction of pharmacokinetics is not possible. Some evaluation of hepatic function is possible by assessing serum albumin and bilirubin, and prothrombin time. However, these parameters are not directly related to drug clearance. Although not directly correlated with liver dysfunction, elevated liver enzymes may raise the suspicion of hepatic impairment requiring further investigation.

The Child-Turcotte score was designed to estimate the operative risk of an alcoholic patient with cirrhosis. The parameters used include serum concentrations of bilirubin and albumin, prothrombin time, nutritional status and ascites. These parameters were modified to substitute degree of encephalopathy for nutritional status and then became known as the Child-Pugh classification (see Table 2).[1] The grades A, B and C may also be a useful indicator of an individual's ability to effectively metabolise a drug. An alternative method for assessing liver dysfunction is the Model for End-Stage Liver Disease (MELD) score (www.unos.org/ resources/ MeldPeldCalcu lator.asp).[2] This may be a more accurate method but is less accessible to most clinicians because it involves calculating the score.

Evaluating the drug in question

If a drug is dependent on hepatic elimination, there are several factors to consider when prescribing for patients with liver disease (see box). Determining the hepatic contribution to elimination is paramount and the following general rules should be considered.

Drugs with a narrow therapeutic range that are extensively metabolised by the liver (that is, greater

Table 2

Child-Pugh classification[1]

Parameter	Points assigned = 1	Points assigned = 2	Points assigned = 3
Ascites	Absent	Slight	Moderate
Bilirubin, micromol/L	<11	11-45	>45
Albumin, g/L	>35	28-35	<28
Prothrombin time – seconds over control or INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

Total score of 5-6 is grade A or well compensated disease (1 and 2 year survivals are 100% and 85%)

Total score of 7-9 is grade B or disease with significant functional compromise (1 and 2 year survivals are 80% and 60%)

Total score of 10-15 is grade C or decompensated liver disease (1 and 2 year survivals are 45% and 35%)

Depending on hepatic clearance and the therapeutic index of the drug, dose adjustments or drug avoidance may be required in grades B or C chronic liver disease.

than 20% of their total elimination) should either be avoided altogether (e.g. pethidine) or used with extreme caution (e.g. morphine, theophylline) in patients with significant liver disease.

Drugs with a wide therapeutic range which also undergo extensive hepatic metabolism should be used with caution. In particular, the dosing interval should be increased or the total dose reduced (e.g. carvedilol).

Factors to consider when prescribing drugs dependent on hepatic elimination

- Ascertain how much the drug depends on hepatic metabolism for its elimination from the body.
- Determine the degree of hepatic impairment using the Child-Pugh classification (Table 2), hepatic enzyme levels and possibly an ultrasound of the liver with portal vein Doppler study.
- If there is doubt about the degree of hepatic impairment or the drug has a narrow therapeutic index (that is, the upper dose range for efficacy is close to the lower concentration range of toxicity), then lower the recommended starting dose by approximately 50%, and citrate to effect under careful supervision – 'start low and go slow'.
- Determine possible interactions between the new drug and any drugs the patient is already taking.

If hepatic elimination is limited (that is, accounting for less than 20% of total elimination), then the therapeutic range of the compound should be reviewed. If the drug has a wide therapeutic index, then the likelihood of an adverse effect related to hepatic impairment is low. However, if the drug has a narrow therapeutic index, then caution should be exercised as significant hepatic impairment may have a clinically relevant effect on the pharmacokinetics (e.g. lamotrigine).

If greater than 90% of the compound is excreted unchanged in the urine, then hepatic impairment is unlikely to play a significant role in the accumulation of the drug and therefore toxicity.

Conclusion

Prescribing in hepatic impairment is less well defined when compared to guidelines for prescribing in renal failure. Hepatic dysfunction is less overt and may not be apparent until much of the functioning liver is lost. Knowledge of the metabolism of drugs eliminated by the liver is useful along with close monitoring of the

patient for unwanted adverse effects related to possible toxicity. When introducing long term treatment with a drug with high hepatic clearance or a narrow therapeutic index, assess liver function (clinically and with baseline liver function tests). However, once the drug is commenced routine monitoring is costly and its role unclear in most cases of prescribing in patients with hepatic dysfunction.

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Management of massive blood loss

Massive blood loss is not an uncommon event in the hospital setting. It is seen most often in association with trauma and obstetric practice.

A massive blood loss is defined as

1. loss of one blood volume within 24 hours. (Normal adult blood volume is approximately 70ml/kg, 80ml/kg in children and 90 ml/kg in neonates),
2. loss of 50% blood volume within 3 hours, or
3. a rate of loss of 150ml per minute

Effective and timely management is mandatory to save the patient's life. It poses a challenge to the staff involved, especially in clinical settings where the facilities are not optimal.

The following are required for a successful outcome.

1. Early recognition
2. Prompt action
3. Effective communication among those who are managing the bleed, supplying blood and providing laboratory services.

A multidisciplinary approach involving surgeon, obstetrician, anaesthetist, haematologist and transfusion specialist is essential if a successful outcome is to be achieved.

The therapeutic goals of managing a massive blood loss are:

1. Restoration of blood volume to maintain tissue perfusion and oxygenation

2. Achieve haemostasis by
   a. treating any traumatic, surgical or obstetric source of bleeding.
   b. correcting coagulopathy by judicious use of blood components.

Managing a massive blood loss is an emergency where time is a limiting factor. Therefore it is advisable to adhere to a protocol. The entire management process can be made to run smoothly by appointing a member of the clinical staff to act as a coordinator responsible for overall organisation, liaison, communication and documentation.

The important steps in the management of a massive blood loss are discussed below.

1. Restore circulating volume

It is important to prevent hypovolaemic shock, subsequent multiorgan failure, and disseminated intravascular coagulation (DIC), which carry a high risk of death.

a. Rapid infusion of crystalloids or colloid through 14G peripheral cannulae is recommended. (Whether to use colloid or crystalloid is still controversial, so use what is available).

b. Aim to maintain normal blood pressure and a urine output of 30 ml/hour.

c. Hypothermia increases the risk of end-organ failure and coagulopathy, and it should be prevented by the use of fluid warmers, prewarmed fluid and warm air blankets.

2. Contact key personnel

a. Most appropriate surgical team (eg. surgeon, obstetrician), duty anaesthetist, blood bank, haematologist, laboratory.

b. Appoint a courier/porter for transport of specimens to laboratory and blood bank, and collection of blood products.

3. Start action to arrest bleeding

Apply pressure over a bleeding external wound or attempt to identify source of bleeding by surgical exploration.

4. Request laboratory investigations

a. Full Blood Count (FBC), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, grouping and cross-match, biochemical profile, and blood gases.

b. Repeat FBC, PT, APTT every 4 hours.

The requests should indicate clearly that reports are required urgently and the duty medical laboratory technologist should be informed over the phone of the emergency.

5. Blood component therapy

Red cell concentrates

a. Blood loss is usually underestimated and the haemoglobin (Hb) and haemotocrit (Hct) values do not fall for several hours after acute blood loss. The current recommendation is that blood transfusion is rarely indicated when Hb is >10g/dl, but almost always necessary when it is <6g/dl.

b. Red cell transfusion is likely to be required when 30-40% of the blood volume is lost. Over 40% loss is immediately life threatening. The local practice is to consider red cell transfusion when the loss is >20%. However, if the patient is a child, if the patient was anaemic before the blood loss, is suffering from atherosclerosis, has a poor cardio-respiratory reserve, or if further bleeding is anticipated, transfusion threshold is lowered to >10% loss.

c. Uncrossmatched ABO specific Rh negative blood can be given in an extreme emergency. When the group is identified ABO group specific blood should be given and when time permits, fully compatible blood should be used for transfusion.

Fresh frozen plasma and cryoprecipitate

They must be given after replacement of 1 volume of blood, or before if there is clinical or laboratory evidence of DIC.

Dose:

FFP	15ml/kg BW (1 litre or 4 units for an adult)
Cryoprecipitate	1-1.5 packs/ 10 kg BW

The aim should be to keep PT and APTT <1.5 of mean control and fibrinogen >1g/ l.

Platelets

a. Anticipate the platelets to drop $<50 \times 10^9$/l after replacement of 1.5 volumes of blood, or before in the setting of DIC.

b. The aim should be to maintain the platelets $>75 \times 10^9$ / l or $>100 \times 10^9$ / l in patients with multiple or CNS trauma, or if platelet dysfunction is suspected.

   Dose: One adult therapeutic pack (six packs of single donor unit platelets) or 10 ml/kg body weight for a neonate or small child.

   Another option is to replace blood components at a ratio of 1:1:1(packed red blood cells to fresh frozen plasma to platelet concentrates) from the beginning when a massive blood loss is taking place.

6. Suspect and manage DIC

DIC is a serious complication in an acutely bleeding patient. Patients with prolonged hypoxia, hypovolaemia, hypothermia, and cerebral or extensive muscle damage are at particular risk. It carries a high risk of death and is difficult to reverse once established. Laboratory evidence of DIC should be sought before microvascular bleeding becomes evident, and aggressive action taken to correct the underlying cause.

7. Correct metabolic consequences of massive transfusion

Complex metabolic changes may occur because of hypovolaemia, hypothermia and the infusion of large volumes of stored red cells and blood products.

a. Hypocalcaemia. This occurs from citrate toxicity when large volumes of stored blood components are transfused, particularly in the presence of abnormal liver function, where citrate metabolism is slowed.

   This should be corrected by intravenous infusion of calcium chloride (not gluconate as this requires liver metabolism to release ionized calcium). The recommended dose is 10 ml of 10% calcium chloride.

b. Hyperkalaemia may occur, from the high extracellular potassium concentration in stored red cell units. This may be compounded by oliguria and the metabolic acidosis is associated with shock. If the serum potassium level is >6 mmol/l. The patient should be treated with a glucose-insulin regimen together with bicarbonate to correct the acidosis.

   Early haemofiltration is likely to be required after the arrest of bleeding in the most severe cases.

8. Use of antifibrinolytic drugs to control bleeding

Antifibrinolytic drugs, such as aprotinin and tranexamic acid, can reduce blood loss by retarding or arresting fibrinolysis. Aprotinin has been found to decrease blood loss in certain cardiac, orthopaedic, and transplant surgeries by inhibiting serine proteases, such as plasmin. As the haemostatic abnormalities that occur after injury are similar to those bleeding after surgery, it is possible that antifibrinolytic agents may also reduce blood loss, the need for transfusion, and death following trauma. However, to date there is insufficient evidence on the effect of antifibrinolytic drugs in major trauma to either support or refute a clinically important treatment effect.

9. Consider the use of recombinant Factor VIIa

It is reasonable to consider the use of rVIIa in situations where there is continuous bleeding despite adequate replacement of coagulation factors with FFP, cryoprecipitate and platelets, and where surgical control of bleeding is not possible.

10. Prevent hazards of massive transfusion

The most frequently reported adverse event associated with blood transfusion is giving incompatible blood to the patient, which may result in a fatal haemolytic reaction. The risk of error is particularly high in an emergency. Protocols must be in place for the administration of blood and blood components, and these must be adhered to whatever the degree of urgency.

Transfusion-related acute lung injury (TRALI) and other acute immunologically mediated reactions are uncommon, but occur 5-6 times more frequently following administration of platelets and FFP than following red cells.

Summary

A patient with massive blood loss is best managed by a multidisciplinary team. It would be most appropriate if each hospital has its own protocol based on the available resources to handle such a situation. Protocols should include the functions of each of the disciplines involved displayed or readily available at each of the sites involved (operating theatre, labour room, laboratory, blood bank etc). The main objective of this exercise is to offer the best available care to the patient in the shortest period of time with minimum wastage of resources.

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Management of dengue fever in children

Dengue is the most rapidly spreading viral illness in the world. About 50 million people get infected annually, and about 40% of the world's population live in endemic areas. The Asia-Pacific region carries almost 75% of the disease burden [1].

Dengue has a wide range of clinical presentations, often with unpredictable clinical evolution and outcome. Most patients have a self-limiting clinical course, but a minority will progress to severe disease, characterised by hypovolaemia due to plasma leakage with or without heamorrhage. Although it is difficult to identify those who will progress from non-severe to severe disease, their early identification and providing appropriate treatment will reduce morbidity and mortality. The hallmark of management is close monitoring and timely intervention.

Dengue virus is a single-stranded RNA virus comprising four serotypes (DEN-1 to -4), and belongs to genus *Flavivirus.* It is spread by *Aedes* mosquitoes and mainly by *Ae. aegypti*. Primary infection is thought to induce lifelong protective immunity to the infecting serotype [2]. Individuals suffering from an infection are protected from clinical illness with a different serotype for 2-3 months of the primary infection, but with no long term cross-protective immunity [3,4].

Age, ethnicity, nutritional status and possibly chronic diseases (eg. bronchial asthma, sickle cell anaemia and diabetes mellitus) are some of the factors that determine the severity of disease [3]. Children are less able to compensate for capillary leakage, and are consequently at greater risk of developing dengue shock. Antibody-dependent enhancement (ADE) of infection has been proposed as a mechanism to explain severe dengue [4].

The illness has 3 main phases; febrile, critical and recovery. Changes that occur during these periods are shown in the figure.

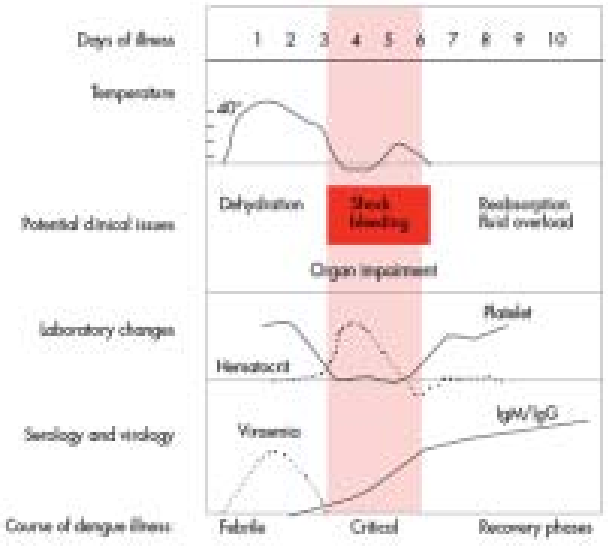

Figure: **Clinical course of dengue fever**
(Reproduced from reference [3]**)**

Febrile phase

All infected children will go through this phase and the vast majority will recover uneventfully. Maintaining a high degree of vigilance and anticipating what may happen will help in cost-effective management and saving lives.

Patients typically develop sudden high fever. This acute febrile phase usually lasts 3-7 days and the first 48-72 hours will be of high intensity. After 2-3days, they may have an afebrile period of about 24 hours, followed by low grade fever (biphasic fever pattern). Fever is often accompanied by erythema and flushing of skin, generalized body ache, myalgia, arthralgia and headache with retrorbital pain [1]. Some patients may have upper respiratory tract symptoms. Anorexia, nausea and vomiting are common. It can be difficult to distinguish dengue clinically from other fevers. A positive tourniquet test in this phase increases the probability of dengue.

Management

The initial phase can be managed as an outpatient. However, during this period some monitoring is required. Parents can be empowered to take care of the child, and educated on warning signs needing urgent medical attention.

It is important to get the exact duration of illness as 24-hour blocks. Many lay people give the number of days inaccurately, grossly over-estimating the duration. (eg. patient presenting on a Wednesday morning with fever that started on Monday night will state it is the third day of fever, but the actual duration is one and a half days). Such misinterpretation of duration will lead to wrong anticipation of the critical phase, or to suppose that the critical period is over, relax monitoring and delay detection of severe complications. Another important part in the management is timing of the blood tests. A full blood count (FBC) on the first day of illness, could be misleading as the initial response is a neutrophilia, which may be interpreted as a bacterial infection. The most important part is assessment of the clinical condition. If the child is relatively well between fever spikes, it is most likely due to a viral infection, and requesting a full blood count after 48 hours from the onset of illness would give a better picture of the disease. If the child has a leucopenia ($<5000mm^{-3}$) with relative lymphocytosis, that is suggestive of dengue. Furthermore the platelet count could be low or in the lower normal range. If the platelet count is above 100 $000mm^{-3}$, but shows a downward trend, repeat it at 12 hourly intervals.

Fever can be controlled with paracetamol (10-15 mg/kg/ dose at 6 hourly intervals or as required). The most important part of home management is administration of adequate liquids. It could be a mixture of water, oral rehydration solution, fruit juices (king coconut, lime, lemon etc) or cunjee. A minimum rate of about 4-5 ml/kg/hour while awake is satisfactory. Avoid red or brown coloured food as they could mimic blood if the child vomits. If vomiting is present, start on oral domperidone (0.4 mg/kg/dose) and continue 8 hourly for about 24 hours. The child needs adequate rest even if he is comfortable and wants to play.

Parents should be informed about the warning symptoms needing hospitalisation. Abdominal pain, persistent vomiting, cold extremities, bleeding (haematemesis, melaena), lethargy, restlessness, irritability, drowsiness, dyspnoea, and not passing urine for >5 hours are feature that warrant immediate admission.

Detection of tender hepatomegaly (>2cm), pleural effusion, a positive tourniquet test, poor peripheral circulation or laboratory investigations showing raised haematocrit (>40%), platelet count ≤100 $000mm^{-3}$, severe leucopenia (WBC $<2000mm^{-3}$), or elevated ALT/AST need urgent admission.

After admission the following variables need close monitoring:

- Temperature four-hourly
- Pulse, blood pressure, respiratory rate, and capillary refill time – two-hourly (may need more frequently depending on the clinical situation)
- Fluid intake and output
- FBC daily (and twice daily platelet count when it is <150 000mm^{-3})
- Haematocrit 12 or 8 hourly depending on state of fluid leak and resuscitation

Critical phase

Between 3 and 6 days of illness the child may show some improvement in the temperature. During this period an increase in capillary permeability in parallel with increasing haematocrit may occur [5]. With the platelet count <100 000mm^{-3} and presence of a 20% or more rise in the haematocrit from base line (from the initial result or in the absence of a previous value, consider baseline for children as 35%), or objective evidence of fluid leak (pleural effusion/ascites), or serum albumin of <3.5g/dl, or cholesterol of <100 mg/dl, marks the beginning of the critical phase.

The period of clinically significant plasma leakage usually lasts 24-48 hours. Progressive leucopenia followed by a rapid decrease in platelet count usually precedes this phase [6], and the child should be managed in a hospital. Most important aspect of management is intensifying the monitoring of vital signs.

Fever should be controlled with paracetamol; avoid NSAIDs. Domperidone can be used to control vomiting. If the child tolerates oral feeds continue oral fluids at about 2 ml/kg/hour. Keep an IV cannula in situ. If oral intake is low (or when the child is sleeping) start an IV drip. Isotonic saline with 5% dextrose is suitable as a maintenance drip at a rate of 1.5-2 ml/kg/hour. However, rates should be titrated to maintain vital signs within acceptable limits, and especially, to maintain a urine output of 0.5-1.0 ml/kg/hour.

Blood should be sent for FBC, ALT, AST, blood grouping, serum electrolytes, serum calcium as a baseline, and repeated appropriately. Haematocrit and platelet counts should be repeated at 8 and 12 hourly intervals to assess progress.

Fluid management

Appropriate fluid management is the key to successful outcome. Over-enthusiastic fluid delivery leads to many complications. The fluid in the body is only redistributed, and when the critical period is over, the extravasated fluid will return to the vascular compartment leading to fluid overload and exerting a massive strain on the heart. Hence fluid should be administered cautiously to maintain the vital signs within acceptable limits.

Fluids should be given to maintain adequate organ perfusion (stable conscious level), pulse rate ≤100 / min, capillary refill time ≤2 sec, blood pressure within normal limits with a pulse pressure ≥20 mmHg, urine output at 0.5-1 ml/kg/hour, and to minimise metabolic acidosis. In order to maintain the vital signs, drips may have to be increased even up to 7 ml/kg/h. Once the patient is stable, consider as soon as possible, to lower the infusion rate while maintaining vital signs.

To prevent fluid overload, a fluid quota system is introduced. It is the total fluid volume to be administered during the 48 hour critical phase. It is one day's normal fluid requirement plus 5%. The calculating weight should either be the ideal weight for the height of the child or actual weight whichever is lower. Fluid volume is calculated using Holliday and Segar equation (panel 1) [7]. This is the maximum fluid volume that is allowed during this period. It is not mandatory to give this entire volume, but only the amount required to serve the purpose. Crystalloids are used as the replacement fluid. The mode and rate of fluid administration should be revised at 4-6 hour intervals. This will prevent under perfusion and fluid overload.

Panel 1. Calculation of total fluid quota for critical period [7]

Maintenance	100 ml/kg for first 10 kg
	50 ml/kg for second 10 kg
	20 ml/kg for balance weight
5% deficit	50 ml × body weight (kg)

Management of shock

Fluid extravasation may be so severe that physiological adaptation will become insufficient, and the patient will develop inadequate tissue perfusion leading to hypoxia. Initially tissue perfusion could be low but blood pressure

is maintained, with very narrow pulse pressure, and this state is known as "compensatory shock". But if supportive measures are not taken, patients will progress to profound or "hypotensive shock", where pulse and BP are unrecordable (table 1) [3].

Management

Shock with narrow pulse pressure or compensated shock

Initially give isotonic saline 10 ml/kg over an hour and if there is no improvement, repeat the same volume. If there is no improvement after 2 boluses, then give a colloid (Dextran 40 or 6% heta starch) bolus 10 ml/kg over an hour. When a response is shown after any of the infusions, change to saline (if child was on colloids), and step down the infusion rate, while maintaining vital signs. If there was no response after colloid infusion and haematocrit is rising, repeat 1-2 colloid boluses as above. If it is dropping with no improvement in shock, give a blood transfusion of 10 ml/kg.

Profound shock or hypotensive shock

In profound shock, give isotonic saline bolus of 20 ml/kg over 15 minutes and repeat the same dose if there is no response. If still there is no response, give a colloid bolus 10 ml/kg over an hour. When a response is shown after any of the infusions change to saline (if child was on colloids), and step down the infusion rate guided by vital signs. If there was no response after colloid bolus and haematocrit is rising, repeat 1-2 colloid boluses as above. If it is dropping with no improvement in shock give a blood transfusion of 10 ml/kg.

Table: Assessment of haemodynamic state

Sign	*Stable circulation*	*Compensated shock*	*Hypotensive shock*
Mental state	Clear and lucid	Clear and lucid (if you do not touch may miss poor peripheral circulation)	Change of mental status (restless and combative)
Capillary refill time	Brisk (<2 sec)	Prolonged (>2sec)	Very prolonged, and mottled skin
Extremities	Warm and pink	Cold	Cold and clammy. If pressure is exerted, long time to regain original skin colour and cold line is detectable
Peripheral pulse	Good	Weak and thready	Feeble or difficult to feel
Heart rate (interpret keeping state of fever in mind)	Normal for age	Tachycardia	Severe tachycardia with bradycardia in late shock
Blood pressure	Normal SBP and DBP for age. Pulse pressure >20 mmHg	Normal SBP or slightly low. Rising DBP. Pulse pressure <20 mmHg	Narrow pulse pressure <20 mmHg Hypotension* Unrecordable pressure
Respiration	Normal	Tachypnea	Metabolic acidosis Hyperpnoea/ Kussmaul breathing

*In children <10 years the SBP <5th centile for age, sex and height centile, or calculate using the following formula; 70+ (Age in years × 2) mmHg
Older children or adults SBP <90 mmHg or mean arterial pressure <70 mmHg or SBP decrease by >40 mmHg for age.
(SBP = Systilic BP: DBP + diastolic BP)

Recovery phase

If the patient survives the 24-48 hour critical phase, a gradual reabsorption of extravasated fluid will take place during the next 48-72 hours. During the convalescence most children will experience an intense pruritus, especially in the palms and soles. General well-being and irritability improve, vomiting stops, appetite improves, haemodynamic status stabilises, and diuresis begins. Some patients may have a rash of "isles of white in a sea of red" [3]. Blood pressure could be in the high normal centiles. During this phase IV fluid should be stopped and oral fluids started. If signs of fluid overload are present (difficulty in breathing, tachypnea, wheezing, large pleural effusions (chest x ray or ultrasound scan will assist in confirmation), tense ascites, increased jugular venous pressure) a diuretic should be given. Oral (1-2 mg/kg /dose) or IV (0.5-1mg/kg/dose) frusemide can be given and repeated if necessary. The recovery phase also needs active management as hypervolaemia could lead to complications.

Severe dengue

Severe dengue is defined by one or more of the following: (i) plasma leakage that may lead to shock (dengue shock) and fluid accumulation, with or without respiratory distress, and (ii) severe bleeding, and (iii) severe organ impairment [3]. Usually these occur on days 4-5 of illness, preceded by the warning signs.

Children with severe dengue may have coagulation abnormalities, but these are usually not sufficient to cause major bleeding. Major bleeding is almost always associated with profound shock. The combination of thrombocytopenia, hypoxia and acidosis, will lead to multiple organ failure with advanced disseminated intravascular coagulation [3]. Unusual manifestations are acute liver failure, cardiomyopathy, encephalopathy and encephalitis. However, most deaths from dengue occur in patients with profound shock, particularly if the situation is complicated by fluid overload [3].

The child may need high dependency or intensive care when shock presents during the first 2-3 days of illness, severe plasma leakage, very low volume pulse and unrecordable blood pressure, severe bleeding, fluid overload (pleural effusion, pulmonary oedema, ascites), or organ dysfunction (hepatic damage, cardiomyopathy, encephalopathy, renal failure).

Other complications of dengue

Both hyperglycaemia and hypoglycaemia can occur. Electrolyte and acid-base imbalances are also common, usually related to gastrointestinal losses or the use of hypotonic solutions. Other electrolyte imbalances are hyponatraemia, hypokalaemia, hyperkalaemia, serum calcium disturbances and metabolic acidosis. The clinician should also be alert for co-infections and nosocomial infections. Checking for **A**cidosis, **B**leeding, **C**alcium and **S**ugar (ABCS) during the critical period is important.

Notification

Notification is mandatory for early detection of new cases and to control spread of the disease.

Confirmatory investigations

A definitive diagnosis of dengue fever is important for epidemiological purposes. Although viral antigens could be checked in the first 48 hours of the febrile phase, a negative result will not rule out dengue. It may give a false sense of security and relax monitoring leading to dire consequences. The better test is to check for dengue antibodies (IgG and IgM) after 5 days of the illness.

Intravenous solutions

There is no clear advantage in the use of colloids over crystalloids in regard to overall outcome in the management of dengue shock [8,9]. However, a hypertonic solution is preferred as it will help to hold fluid in the intravascular compartment for a longer period, thus delaying the leak. Colloids (Dextran 70 or 6% hydroxyethyl starch) may be given if the blood pressure has to be restored urgently, ie. in those with pulse pressure less than 10 mmHg. Colloids have been shown to restore the cardiac index and reduce the haematocrit faster than crystalloids in patients with intractable shock [8,9].

Crystalloids

Isotonic saline is a suitable option for initial fluid resuscitation, but repeated large volumes may lead to hyperchloraemic acidosis, which may aggravate or be confused with lactic acidosis from prolonged shock. Monitoring the chloride and lactate levels will help to identify this problem. When serum chloride is normal, it is advisable to change to Ringer-Lactate.

Ringer-Lactate has lower sodium (131 mmol/l) and chloride (115 mmol/l), and an osmolality of 273 mOsm/l. It is not suitable for resuscitation of patients with severe hyponatraemia [8]. It is a suitable solution after saline has been given and the serum chloride level has exceeded the normal range.

Colloids

Colloids are gelatin-based, dextran-based or starch-based solutions. One of the biggest concerns regarding their use is their effect on coagulation. Theoretically, dextran binds to von Willebrand factor/Factor VIII complex and impairs coagulation, but this was not observed to have clinical significance in fluid resuscitation in dengue shock [9]. Of all the colloids, gelatin has the least effect on coagulation but the highest risk of allergic reactions (fever, chills and rigors). These were also observed with Dextran 70. Dextran 40 can potentially cause an osmotic renal injury in hypovolaemic patients.

Up to 3 doses of Dextran 40 (each as 10 ml/kg/hour) during a 24 hour period (6 doses within 48 hours) and up to 5 doses of 6% hetastarch (each as 10 ml/kg/hour) per 24 hours (10 doses within 48 hours) could be safely given [3].

Blood and blood products

Blood transfusions

Blood transfusion is life-saving and should be given as soon as severe bleeding is suspected or recognised. Blood transfusion must be given with care because of the risk of fluid overload. Do not wait for the Hct to drop too low before deciding on blood transfusion.

Platelet transfusion

It should be noted that prophylactic platelet transfusions for severe thrombocytopenia in otherwise haemodynamically stable patients are not effective and not necessary [10].

FFP transfusion

There is no place for routine use of FFP in the management of dengue patients.

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Self-assessment questions

(And clinical physiology in small doses)

Select the **best** response to each question

1. Which of the following statements regarding the liver is true?
   a. The right hemiliver has 3 segments in all and the left hemiliver has 2 segments, demarcated by divisions of the right, middle and left hepatic veins.
   b. The caudate lobe is situated in the left lobe of the liver.
   c. The caudate lobe is an autonomous segment supplied by independent branches of the hepatic artery and portal vein.
   d. About 40% of the blood supply to the liver comes from the hepatic artery.
   e. The normal portal pressure is 15-20 mmHg.

2. Regarding biochemical tests pertaining to liver function:
   a. aspartate aminotransferase (AST) is primarily a cytosol enzyme specific to liver.
   b. alanine aminotransferase (ALT) is a cytosol enzyme specific to liver.
   c. alkaline phosphatase (ALP) is a mitochondrial enzyme found in hepatocytes.
   d. gamma-glutamyl transpeptidase (λ-GT) is a cytosol enzyme.
   e. 5-nucleotidase, ALP and λ-GT serum levels rise in parallel in non-alcoholic fatty liver disease.

3. Between day 3 and day 6 of the illness in a child with dengue fever, the beginning of the critical phase is signaled by one or more of the following criteria.
   a. Platelet count > 200 000/mm^3 (200×10^9 / litre).
   b. A 5-10% rise of haematocrit over base line value.
   c. A rise in rectal or oral temperature over 38.5°C.
   d. Serum albumin between 3.8-4.2 g/dl.
   e. Objective evidence of pleural effusion and/or ascites.

4. Optimum fluid delivery during the critical phase of dengue fever with capillary leakage in a child should conform to the following criteria.
   a. Capillary fill time ≤ 2 seconds.
   b. Urine output over 2.5 ml / kg / hour.
   c. Pulse rate between 100 and 115 / min.
   d. Pulse pressure between 10 and 20 mmHg.
   e. Body temperature between 37.5 and 38.5 °C.

Answers to self-assessment questions

Question 1. The correct response is **c.** The right hemiliver as 4 segments and the left 3. The caudate lobe is in the right lobe, but has an independent blood supply. Its venous drainage is by 2 separate veins to the inferior vena cava. Hence it is referred to as an 'autonomous segment'. The hepatic artery supplies only 20-25% of the liver's blood supply and the normal portal vein pressure is 5-8 mmHg.

Question 2. The correct response is **b.** AST is a mainly a mitochondrial enzyme, also found in heart, kidney, brain, muscle etc. ALT is a cytosol enzyme more specific to liver and it rises in blood only in liver disease. ALP is found in canalicular and sinusoidal membranes in liver – not in hepatocytes. λ-GT is a microsomal enzyme, and so is 5-nucleotidase. The latter, ALP and λ-GT levels in serum do not rise in parallel in NAFLD.

Question *3. The correct response is **e.** The other criteria are: platelet count ≤ 100 000; 20% or more rise in haematocrit; serum albumin ≤ 3.5 g/dl. The temperature is not a valid criterion by itself. So responses a-d are factually incorrect.

Question *4. The correct response is **a.** Responses b-e are factually incorrect.

*See article by Dr. Wickramasinghe in this issue of *SLP* for detailed management of dengue fever in children.

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