Chapter 2

Shock and blood transfusion

Learning objectives

To understand:

- The pathophysiology of shock and ischaemia–reperfusion injury
- The different patterns of shock and the principles and priorities of resuscitation
- Appropriate monitoring and end points of resuscitation
- Use of blood and blood products, the benefits and risks of blood transfusion

INTRODUCTION

Shock is the most common and therefore the most important cause of death of surgical patients. Death may occur rapidly due to a profound state of shock, or be delayed due to the consequences of organ ischaemia and reperfusion injury. It is important therefore that every surgeon understands the pathophysiology, diagnosis and priorities in management of shock and haemorrhage.

SHOCK

Shock is a systemic state of low tissue perfusion that is inadequate for normal cellular respiration. With insufficient delivery of oxygen and glucose, cells switch from aerobic to anaerobic metabolism. If perfusion is not restored in a timely fashion, cell death ensues.

Pathophysiology

Cellular

As perfusion to the tissues is reduced, cells are deprived of oxygen and must switch from aerobic to anaerobic metabolism. The product of anaerobic respiration is not carbon dioxide but lactic acid. When enough tissue is underperfused, the accumulation of lactic acid in the blood produces a systemic metabolic acidosis.

As glucose within cells is exhausted, anaerobic respiration ceases and there is failure of sodium/potassium pumps in the cell membrane and intracellular organelles. Intracellular lysosomes release autodigestive enzymes and cell lysis ensues. Intracellular contents, including potassium, are released into the blood stream.

Microvascular

As tissue ischaemia progresses, changes in the local milieu result in activation of the immune and coagulation systems. Hypoxia and acidosis activate complement and prime neutrophils, resulting in the generation of oxygen free radicals and cytokine release. These mechanisms lead to injury of the capillary endothelial cells. These, in turn, further activate the immune and coagulation systems. Damaged endothelium loses its integrity and becomes 'leaky'. Spaces between endothelial cells allow fluid to leak out and tissue oedema ensues, exacerbating cellular hypoxia.

Systemic

CARDIOVASCULAR

As preload and afterload decrease, there is a compensatory baroreceptor response resulting in increased sympathetic activity and release of catecholamines into the circulation. This results in tachycardia and systemic vasoconstriction (except in sepsis – see below).

RESPIRATORY

The metabolic acidosis and increased sympathetic response result in an increased respiratory rate and minute ventilation to increase the excretion of carbon dioxide (and so produce a compensatory respiratory alkalosis).

RENAL

Decreased perfusion pressure in the kidney leads to reduced filtration at the glomerulus and a decreased urine output. The renin–angiotensin–aldosterone axis is stimulated, resulting in further vasoconstriction and increased sodium and water reabsorption by the kidney.

ENDOCRINE

As well as activation of the adrenal and renin–angiotensin systems, vasopressin (antidiuretic hormone) is released from the hypothalamus in response to decreased preload and results in vasoconstriction and resorption of water in the renal collecting system. Cortisol is also released from the adrenal cortex, contributing to the sodium and water resorption and sensitising cells to catecholamines.

Ischaemia–reperfusion syndrome

During the period of systemic hypoperfusion, cellular and organ damage progresses due to the direct effects of tissue hypoxia and local activation of inflammation. Further injury occurs once normal circulation is restored to these tissues. The acid and potassium load that has built up can lead to direct myocardial depression, vascular dilatation and further hypotension. The cellular and humoral elements activated by the hypoxia (complement, neutrophils, microvascular thrombi) are flushed back into the circulation where they cause further endothelial injury to organs such as the lungs and the kidneys. This leads to acute lung injury, acute renal injury, multiple organ failure and death. Reperfusion injury can currently only be attenuated by reducing the extent and duration of tissue hypoperfusion.

Classification of shock

There are numerous ways to classify shock, but the most common and most clinically applicable is one based on the initiating mechanism.

All states are characterised by systemic tissue hypoperfusion, and different states may coexist within the same patient.

Summary box 2.1

Classification of shock

- Hypovolaemic shock
- Cardiogenic shock
- Obstructive shock
- Distributive shock
- Endocrine shock

Hypovolaemic shock

Hypovolaemic shock is due to a reduced circulating volume. Hypovolaemia may be due to haemorrhagic or non-haemorrhagic causes. Non-haemorrhagic causes include poor fluid intake (dehydration), excessive fluid loss due to vomiting, diarrhoea, urinary loss (e.g. diabetes), evaporation, or 'third-spacing' where fluid is lost into the gastrointestinal tract and interstitial spaces, as for example in bowel obstruction or pancreatitis.

Hypovolaemia is probably the most common form of shock, and to some degree is a component of all other forms of shock. Absolute or relative hypovolaemia must be excluded or treated in the management of the shocked state, regardless of cause.

Cardiogenic shock

Cardiogenic shock is due to primary failure of the heart to pump blood to the tissues. Causes of cardiogenic shock include myocardial infarction, cardiac dysrhythmias, valvular heart disease, blunt myocardial injury and cardiomyopathy. Cardiac insufficiency may also be due to myocardial depression caused by endogenous factors (e.g. bacterial and humoral agents released in sepsis) or exogenous factors, such as pharmaceutical agents or drug abuse. Evidence of venous hypertension with pulmonary or systemic oedema may coexist with the classical signs of shock.

Obstructive shock

In obstructive shock there is a reduction in preload due to mechanical obstruction of cardiac filling. Common causes of obstructive shock include cardiac tamponade, tension pneumothorax, massive pulmonary embolus or air embolus. In each case, there is reduced filling of the left and/or right sides of the heart leading to reduced preload and a fall in cardiac output.

Distributive shock

Distributive shock describes the pattern of cardiovascular responses characterising a variety of conditions, including septic shock, anaphylaxis and spinal cord injury. Inadequate organ perfusion is accompanied by vascular dilatation with hypotension, low systemic vascular resistance, inadequate afterload and a resulting abnormally high cardiac output.

In anaphylaxis, vasodilatation is due to histamine release, while in high spinal cord injury there is failure of sympathetic outflow and adequate vascular tone (neurogenic shock). The cause in sepsis is less clear but is related to the release of bacterial products (endotoxin) and the activation of cellular and humoral components of the immune system. There is maldistribution of blood flow at a microvascular level with arteriovenous shunting and dysfunction of cellular utilization of oxygen.

In the later phases of septic shock there is hypovolaemia from fluid loss into interstitial spaces and there may be concomitant myocardial depression, complicating the clinical picture (*Table 2.1*).

Endocrine shock

Endocrine shock may present as a combination of hypovolaemic, cardiogenic or distributive shock. Causes of endocrine shock include hypo- and hyperthyroidism and adrenal insufficiency. Hypothyroidism causes a shock state similar to that of neurogenic shock due to disordered vascular and cardiac responsiveness to circulating catecholamines. Cardiac output falls due to low inotropy and bradycardia. There may also be an associated cardiomyopathy. Thyrotoxicosis may cause a high-output cardiac failure.

Adrenal insufficiency leads to shock due to hypovolaemia and a poor response to circulating and exogenous catecholamines. Adrenal insufficiency may be due to pre-existing Addison's disease or be a relative insufficiency due to a pathological disease state, such as systemic sepsis.

Thomas Addison, 1799–1860, physician, Guy's Hospital, London, UK, described the effects of disease of the suprarenal capsules in 1849.

TABLE 2.1 Cardiovascular and metabolic characteristics of shock.

	Hypovolaemia	Cardiogenic	Obstructive	Distributive
Cardiac output Vascular resistance	Low High	Low High	Low High	High Low
Venous pressure	Low	High	High	Low
Mixed venous saturation Base deficit	Low High	Low High	Low High	High High

Severity of shock

Compensated shock

As shock progresses, the body's cardiovascular and endocrine compensatory responses reduce flow to non-essential organs to preserve preload and flow to the lungs and brain. In compensated shock, there is adequate compensation to maintain central blood volume and preserve flow to the kidneys, lungs and brain. Apart from a tachycardia and cool peripheries (vasoconstriction, circulating catecholamines), there may be no other clinical signs of hypovolaemia.

However, this cardiovascular state is only maintained by reducing perfusion to the skin, muscle and gastrointestinal tract. There is a systemic metabolic acidosis and activation of humoral and cellular elements within the underperfused organs. Although clinically occult, this state will lead to multiple organ failure and death if prolonged, due to the ischaemia–reperfusion effect described above under **Ischaemia–reperfusion syndrome**. Patients with occult hypoperfusion (metabolic acidosis despite normal urine output and cardiorespiratory vital signs) for more than 12 hours have a significantly higher mortality, infection rate and incidence of multiple organ failure (see below, **Multiple organ failure**).

Decompensation

Further loss of circulating volume overloads the body's compensatory mechanisms and there is progressive renal, respiratory and cardiovascular decompensation. In general, loss of around 15% of the circulating blood volume is within normal compensatory mechanisms. Blood pressure is usually well maintained and only falls after 30–40% of circulating volume has been lost.

Mild shock

Initially there is tachycardia, tachypnoea, a mild reduction in urine output and the patient may exhibit mild anxiety. Blood pressure is maintained although there is a decrease in pulse pressure. The peripheries are cool and sweaty with prolonged capillary refill times (except in septic distributive shock).

Moderate shock

As shock progresses, renal compensatory mechanisms fail, renal perfusion falls and urine output dips below 0.5 mL/kg per hour. There is further tachycardia, and now the blood pressure starts to fall. Patients become drowsy and mildly confused.

Severe shock

In severe shock, there is profound tachycardia and hypotension. Urine output falls to zero and patients are unconscious with laboured respiration.

Pitfalls

The classic cardiovascular responses described (*Table 2.2*) are not seen in every patient. It is important to recognise the limitations of the clinical examination and to recognise patients who are in shock despite the absence of classic signs.

CAPILLARY REFILL

Most patients in hypovolaemic shock will have cool, pale peripheries, with prolonged capillary refill times. However, the actual capillary refill time varies so much in adults that it is not a specific marker of whether a patient is shocked, and patients with short capillary refill times may be in the early stages of shock. In distributive (septic) shock, the peripheries will be warm and capillary refill will be brisk, despite profound shock.

TACHYCARDIA

Tachycardia may not always accompany shock. Patients who are on beta-blockers or who have implanted pacemakers are unable to mount a tachycardia. A pulse rate of 80 in a fit young adult who normally has a pulse rate of 50 is very abnormal. Furthermore, in some young patients with penetrating trauma, where there is haemorrhage but little tissue damage, there may be a paradoxical bradycardia rather than tachycardia accompanying the shocked state.

TABLE 2.2 Clinical features of shock.

	Compensated	Mild	Moderate	Severe
Lactic acidosis	+	++	++	+++
Urine output	Normal	Normal	Reduced	Anuric
Conscious level	Normal	Mild anxiety	Drowsy	Comatose
Respiratory rate	Normal	Increased	Increased	Laboured
Pulse rate	Mild increase	Increased	Increased	Increased
Blood pressure	Normal	Normal	Mild hypotension	Severe hypotension

BLOOD PRESSURE

It is important to recognise that hypotension is one of the last signs of shock. Children and fit young adults are able to maintain blood pressure until the final stages of shock by dramatic increases in stroke volume and peripheral vasoconstriction. These patients can be in profound shock with a normal blood pressure.

Elderly patients who are normally hypertensive may present with a 'normal' blood pressure for the general population but be hypovolaemic and hypotensive relative to their usual blood pressure. Beta-blockers or other medications may prevent a tachycardic response. The diagnosis of shock may be difficult unless one is alert to these pitfalls.

Consequences

Unresuscitatable shock

Patients who are in profound shock for a prolonged period of time become 'unresuscitatable'. Cell death follows from cellular ischaemia and the ability of the body to compensate is lost. There is myocardial depression and loss of responsiveness to fluid or inotropic therapy. Peripherally there is loss of the ability to maintain systemic vascular resistance and further hypotension ensues. The peripheries no longer respond appropriately to vasopressor agents. Death is the inevitable result.

This stage of shock is the combined result of the severity of the insult and delayed, inadequate or inappropriate resuscitation in the earlier stages of shock. Conversely, when patients present in this late stage, and have minimal responses to maximal therapy, it is important that the futility of treatment is recognised and valuable resources are not wasted.

Multiple organ failure

As techniques of resuscitation have improved, more and more patients are surviving shock. Where intervention is timely and the period of shock is limited, patients may make a rapid, uncomplicated recovery. However the result of prolonged systemic ischaemia and reperfusion injury is end-organ damage and multiple organ failure.

Multiple organ failure is defined as two or more failed organ systems. There is no specific treatment for multiple organ failure. Management is supporting of organ systems, with ventilation, cardiovascular support and haemofiltration/dialysis until there is recovery of organ function. Multiple organ failure currently carries a mortality of 60%; thus, prevention is vital by early aggressive identification and reversal of shock.

Summary box 2.2

Effects of organ failure

- Lung: Acute respiratory distress syndrome
- Kidney: Acute renal insufficiency
- Clotting: Coagulopathy
- Cardiac: Cardiovascular failure

RESUSCITATION

Immediate resuscitation manoeuvres for patients presenting in shock are to ensure a patent airway and adequate oxygenation and ventilation. Once 'airway' and 'breathing' are assessed and controlled, attention is directed to cardiovascular resuscitation.

Conduct of resuscitation

Resuscitation should not be delayed in order to definitively diagnose the source of the shocked state. However, the timing and nature of resuscitation will depend on the type of shock and the timing and severity of the insult. Rapid clinical examination will provide adequate clues to make an appropriate first determination, even if a source of bleeding or sepsis is not immediately identifiable. If there is initial doubt about the cause of shock, it is safer to assume the cause is hypovolaemia and begin with fluid resuscitation, and then assess the response.

In patients who are actively bleeding (major trauma, aortic aneurysm rupture, gastrointestinal haemorrhage), it is counterproductive to institute high-volume fluid therapy without controlling the site of haemorrhage. Increasing blood pressure merely increases bleeding from the site while fluid therapy cools the patient and dilutes available coagulation factors. Thus operative haemorrhage control should not be delayed and resuscitation should proceed in parallel with surgery.

Conversely, a patient with bowel obstruction and hypovolaemic shock must be adequately resuscitated before undergoing surgery otherwise the additional surgical injury and hypovolaemia induced during the procedure will exacerbate the inflammatory activation and increase the incidence and severity of end-organ insult.

Fluid therapy

In all cases of shock, regardless of classification, hypovolaemia and inadequate preload must be addressed before other therapy is instituted. Administration of inotropic or chronotropic agents to an empty heart will rapidly and permanently deplete the myocardium of oxygen stores and dramatically reduce diastolic filling and therefore coronary perfusion. Patients will enter the unresuscitatable stage of shock as the myocardium becomes progressively more ischaemic and unresponsive to resuscitative attempts.

First-line therapy, therefore, is intravenous access and administration of intravenous fluids. Access should be through short, wide-bore catheters that allow rapid infusion of fluids as necessary. Long, narrow lines, such as central venous catheters, have too high a resistance to allow rapid infusion and are more appropriate for monitoring than fluid replacement therapy.

Type of fluids

There is continuing debate over which resuscitation fluid is best for the management of shock. There is no ideal resuscitation fluid, and it is more important to understand how and when to administer it. In most studies of shock resuscitation

there is no overt difference in response or outcome between crystalloid solutions (normal saline, Hartmann's solution, Ringer's lactate) or colloids (albumin or commercially available products). Furthermore, there is less volume benefit to the administration of colloids than had previously been thought, with only 1.3 times more crystalloid than colloid administered in blinded trials. On balance, there is little evidence to support the administration of colloids, which are more expensive and have worse side-effect profiles.

Most importantly, the oxygen carrying capacity of crystalloids and colloids is zero. If blood is being lost, the ideal replacement fluid is blood, although crystalloid therapy may be required while awaiting blood products.

Hypotonic solutions (dextrose etc.) are poor volume expanders and should not be used in the treatment of shock unless the deficit is free water loss (e.g. diabetes insipidus) or patients are sodium overloaded (e.g. cirrhosis).

Dynamic fluid response

The shock status can be determined dynamically by the cardiovascular response to the rapid administration of a fluid bolus. In total, 250–500 mL of fluid is rapidly given (over 5–10 minutes) and the cardiovascular responses in terms of heart rate, blood pressure and central venous pressure are observed. Patients can be divided into 'responders', 'transient responders' and 'non-responders'.

Responders have an improvement in their cardiovascular status that is sustained. These patients are not actively losing fluid but require filling to a normal volume status.

Transient responders have an improvement, but this then reverts to the previous state over the next 10–20 minutes. These patients have moderate ongoing fluid losses (either overt haemorrhage or further fluid shifts reducing intravascular volume).

Non-responders are severely volume depleted and are likely to have major ongoing loss of intravascular volume, usually through persistent uncontrolled haemorrhage.

Vasopressor and inotropic support

Vasopressor or inotropic therapy is not indicated as first-line therapy in hypovolaemia. As discussed above, administration of these agents in the absence of adequate preload rapidly leads to decreased coronary perfusion and depletion of myocardial oxygen reserves.

Vasopressor agents (phenylephrine, noradrenaline) are indicated in distributive shock states (sepsis, neurogenic shock) where there is peripheral vasodilatation, and a low systemic vascular resistance, leading to hypotension despite a high cardiac output. Where the vasodilatation is resistant to catecholamines (e.g. absolute or relative steroid deficiency) vasopressin may be used as an alternative vasopressor.

In cardiogenic shock, or where myocardial depression has complicated a shock state (e.g. severe septic shock with low cardiac output), inotropic therapy may be required to increase cardiac output and therefore oxygen delivery. The inodilator dobutamine is the agent of choice.

Monitoring

The **minimum** standard for monitoring of the patient in shock is continuous heart rate and oxygen saturation monitoring, frequent non-invasive blood pressure monitoring and hourly urine output measurements. Most patients will need more aggressive invasive monitoring, including central venous pressure and invasive blood pressure monitoring.

Summary box 2.3

Monitoring for patients in shock

Minimum

- ECG
- Pulse oximetry
- Blood pressure
- Urine output

Additional modalities

- Central venous pressure
- Invasive blood pressure
- Cardiac output
- Base deficit and serum lactate

Cardiovascular

Cardiovascular monitoring at minimum should include continuous heart rate (ECG), oxygen saturation and pulse waveform and non-invasive blood pressure. Patients whose state of shock is not rapidly corrected with a small amount of fluid should have central venous pressure monitoring and continuous blood pressure monitoring through an arterial line.

CENTRAL VENOUS PRESSURE

There is no 'normal' central venous pressure (CVP) for a shocked patient, and reliance cannot be placed on an individual pressure measurement to assess volume status. Some patients may require a CVP of 5 cmH_2O, whereas some may require a CVP of 15 cmH_2O or higher. Further, ventricular compliance can change from minute to minute in the shocked state, and CVP is a poor reflection of end diastolic volume (preload).

CVP measurements should be assessed dynamically as response to a fluid challenge (see above). A fluid bolus (250–500 mL) is infused rapidly over 5–10 minutes.

The normal CVP response is a rise of 2–5 cmH_2O which gradually drifts back to the original level over 10–20 minutes. Patients with no change in their CVP are empty and require further fluid resuscitation. Patients with a large, sustained rise in CVP have high preload and an element of cardiac insufficiency or volume overload.

Alexis Frank Hartmann, 1898–1964, paediatrician, St Louis, MO, USA, described the solution; should not be confused with the name of Henri Albert Charles Antoine Hartmann, French surgeon, who described the operation that goes by his name.
Sidney Ringer, 1835–1910, Professor of Clinical Medicine, University College Hospital, London, UK.

CARDIAC OUTPUT

Cardiac output monitoring allows assessment of not only the cardiac output but also the systemic vascular resistance and, depending on the technique used, end diastolic volume (preload) and blood volume. Use of invasive cardiac monitoring with pulmonary artery catheters is becoming less frequent as new non-invasive monitoring techniques, such as Doppler ultrasound, pulse waveform analysis and indicator dilution methods, provide similar information without many of the drawbacks of more invasive techniques.

Measurement of cardiac output, systemic vascular resistance and preload can help distinguish the types of shock present (hypovolaemia, distributive, cardiogenic), especially when they coexist. The information provided guides fluid and vasopressor therapy by providing real-time monitoring of the cardiovascular response.

Measurement of cardiac output is desirable in patients who do not respond as expected to first-line therapy, or who have evidence of cardiogenic shock or myocardial dysfunction. Early consideration should be given to instituting cardiac output monitoring for patients who require vasopressor or inotropic support.

Systemic and organ perfusion

Ultimately, the goal of treatment is to restore cellular and organ perfusion. Ideally, therefore, monitoring of organ perfusion should guide the management of shock. The best measure of organ perfusion and the best monitor of the adequacy of shock therapy remains the urine output. However, this is an hourly measure and does not give a minute-to-minute view of the shocked state. The level of consciousness is an important marker of cerebral perfusion, but brain perfusion is maintained until the very late stages of shock, and hence is a poor marker of adequacy of resuscitation (*Table 2.3*).

Currently, the only clinical indicators of perfusion of the gastrointestinal tract and muscular beds are the global measures of lactic acidosis (lactate and base deficit) and the mixed venous oxygen saturation.

BASE DEFICIT AND LACTATE

Lactic acid is generated by cells undergoing anaerobic respiration. The degree of lactic acidosis, as measured by serum lactate level and/or the base deficit, is sensitive for both diagnosis of shock and monitoring the response to therapy. Patients with a base deficit over 6 mmol/L have a much higher morbidity and mortality than those with no metabolic acidosis. Furthermore, the length of time in shock with an increased base deficit is important, even if all other vital signs have returned to normal (see occult hypoperfusion below under **End points of resuscitation**).

These parameters are measured from arterial blood gas analyses, and therefore the frequency of measurements is limited and they do not provide minute-to-minute data on systemic perfusion or the response to therapy. Nevertheless, the base deficit and/or lactate should be measured routinely in these patients until they have returned to normal levels.

MIXED VENOUS OXYGEN SATURATION

The percentage saturation of oxygen returning to the heart from the body is a measure of the oxygen delivery and extraction by the tissues. Accurate measurement is via analysis of blood drawn from a long central line placed in the right atrium. Estimations can be made from blood drawn from lines in the superior vena cava, but these values will be slightly higher than those of a mixed venous sample (as there is relatively more oxygen extraction from the lower half of the body). Normal mixed venous oxygen saturation levels are 50–70%. Levels below 50% indicate inadequate oxygen delivery and increased oxygen extraction by the cells. This is consistent with hypovolaemic or cardiogenic shock.

High mixed venous saturations (>70%) are seen in sepsis and some other forms of distributive shock. In sepsis, there is disordered utilisation of oxygen at the cellular level, and arteriovenous shunting of blood at the microvascular level. Therefore, less oxygen is presented to the cells, and those cells cannot utilise what little oxygen is presented. Thus, venous blood has a higher oxygen concentration than normal.

TABLE 2.3 Monitors for organ/systemic perfusion.

	Clinical	Investigational
Systemic perfusion		Base deficit
		Lactate
		Mixed venous oxygen saturation
Organ perfusion		
Muscle	–	Near-infrared spectroscopy
		Tissue oxygen electrode
Gut	–	Sublingual capnometry
		Gut mucosal pH
		Laser Doppler flowmetry
Kidney	Urine output	–
Brain	Conscious level	Tissue oxygen electrode
		Near-infrared spectroscopy

Christian Johann Doppler, 1803–1853, Professor of Experimental Physics, Vienna, Austria, enunciated the Doppler principle in 1842.

Patients who are septic should therefore have mixed venous oxygen saturations above 70%; below this level, they are not only in septic shock but also in hypovolaemic or cardiogenic shock. Although the S_vO_2 level is in the 'normal' range, it is low for the septic state, and inadequate oxygen is being supplied to cells that cannot utilise oxygen appropriately. This must be corrected rapidly. Hypovolaemia should be corrected with fluid therapy, and low cardiac output due to myocardial depression or failure should be treated with inotropes (dobutamine), to achieve a mixed venous saturation greater than 70% (normal for the septic state).

New methods for monitoring regional tissue perfusion and oxygenation are becoming available, the most promising of which are muscle tissue oxygen probes, near-infrared spectroscopy and sublingual capnometry. While these techniques provide information regarding perfusion of specific tissue beds, it is as yet unclear whether there are significant advantages over existing measurements of global hypoperfusion (base deficit, lactate).

End points of resuscitation

It is much easier to know when to start resuscitation than when to stop. Traditionally, patients have been resuscitated until they have a normal pulse, blood pressure and urine output. However, these parameters are monitoring organ systems whose blood flow is preserved until the late stages of shock. A patient therefore may be resuscitated to restore central perfusion to the brain, lungs and kidneys and yet continue to underperfuse the gut and muscle beds. Thus, activation of inflammation and coagulation may be ongoing and lead to reperfusion injury when these organs are finally perfused, and ultimately multiple organ failure.

This state of normal vital signs and continued underperfusion is termed 'occult hypoperfusion'. With current monitoring techniques, it is manifested only by a persistent lactic acidosis and low mixed venous oxygen saturation. The time spent by patients in this hypoperfused state has a dramatic effect on outcome. Patients with occult hypoperfusion for more than 12 hours have two to three times the mortality of patients with a limited duration of shock.

Resuscitation algorithms directed at correcting global perfusion end points (base deficit, lactate, mixed venous oxygen saturation) rather than traditional end points have been shown to improve mortality and morbidity in high-risk surgical patients. However, it is clear that, despite aggressive regimes, some patients cannot be resuscitated to normal parameters within 12 hours by fluid resuscitation alone. More research is underway to identify the pathophysiology behind this and investigate new therapeutic options.

HAEMORRHAGE

Haemorrhage must be recognised and managed aggressively to reduce the severity and duration of shock and avoid death and/or multiple organ failure. Haemorrhage is treated by arresting the bleeding – not by fluid resuscitation or blood transfusion. Although necessary as supportive measures to maintain organ perfusion, attempting to resuscitate patients who have ongoing haemorrhage will lead to physiological exhaustion (coagulopathy, acidosis and hypothermia) and subsequently death.

Pathophysiology

Haemorrhage leads to a state of hypovolaemic shock. The combination of tissue trauma and hypovolaemic shock leads to the development of an endogenous coagulopathy called acute traumatic coagulopathy (ATC). Up to 25% of trauma patients develop ATC within minutes of injury and it is associated with a four-fold increase in mortality. It is likely that ATC exists whenever there is the combination of shock and tissue trauma (e.g. major surgery). ATC is a component of trauma-induced coagulopathy (TIC), which is ultimately multifactorial (**Figure 2.1**).

Ongoing bleeding with fluid and red blood cell resuscitation leads to a dilution of coagulation factors which worsens the coagulopathy. In addition, the acidosis induced by the hypoperfused state leads to decreased function of the coagulation proteases, resulting in coagulopathy and further haemorrhage. The reduced tissue perfusion includes reduced blood supply to muscle beds. Underperfused muscle is unable to generate heat and hypothermia ensues. Coagulation functions poorly at low temperatures and there is further haemorrhage, further hypoperfusion and worsening acidosis and hypothermia. These three factors result in a downward spiral leading to physiological exhaustion and death (**Figure 2.1**).

Medical therapy has a tendency to worsen this effect. Intravenous blood and fluids are cold and exacerbate hypothermia. Further heat is lost by opening body cavities during surgery. Surgery usually leads to further bleeding and many crystalloid fluids are themselves acidic (e.g. normal saline has a pH of 6.7). Every effort must therefore be made to rapidly identify and stop haemorrhage, and to avoid (preferably) or limit physiological exhaustion from coagulopathy, acidosis and hypothermia.

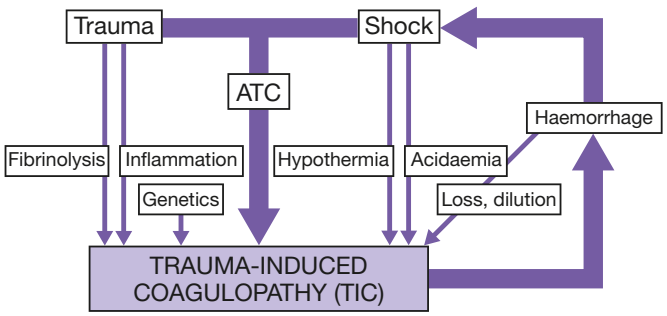

Figure 2.1 Trauma-induced coagulopathy.

Definitions

Revealed and concealed haemorrhage

Haemorrhage may be revealed or concealed. Revealed haemorrhage is obvious external haemorrhage, such as exsanguination from an open arterial wound or from massive haematemesis from a duodenal ulcer.

Concealed haemorrhage is contained within the body cavity and must be suspected, actively investigated and controlled. In

trauma, haemorrhage may be concealed within the chest, abdomen, pelvis, retroperitoneum or in the limbs with contained vascular injury or associated with long-bone fractures. Examples of non-traumatic concealed haemorrhage include occult gastrointestinal bleeding or ruptured aortic aneurysm.

Primary, reactionary and secondary haemorrhage

Primary haemorrhage is haemorrhage occurring immediately due to an injury (or surgery). Reactionary haemorrhage is delayed haemorrhage (within 24 hours) and is usually due to dislodgement of a clot by resuscitation, normalisation of blood pressure and vasodilatation. Reactionary haemorrhage may also be due to technical failure, such as slippage of a ligature.

Secondary haemorrhage is due to sloughing of the wall of a vessel. It usually occurs 7–14 days after injury and is precipitated by factors such as infection, pressure necrosis (such as from a drain) or malignancy.

Surgical and non-surgical haemorrhage

Surgical haemorrhage is due to a direct injury and is amenable to surgical control (or other techniques such as angioembolisation). Non-surgical haemorrhage is the general ooze from all raw surfaces due to coagulopathy and cannot be stopped by surgical means (except packing). Treatment requires correction of the coagulation abnormalities.

Degree and classification

The adult human has approximately 5 litres of blood (70 mL/kg children and adults, 80 mL/kg neonates). Estimation of the amount of blood that has been lost is difficult, inaccurate and usually underestimates the actual value.

External haemorrhage is obvious, but it may be difficult to estimate the actual volume lost. In the operating room, blood collected in suction apparatus can be measured and swabs soaked in blood weighed.

The haemoglobin level is a poor indicator of the degree of haemorrhage because it represents a concentration and not an absolute amount. In the early stages of rapid haemorrhage, the haemoglobin concentration is unchanged (as whole blood is lost). Later, as fluid shifts from the intracellular and interstitial spaces into the vascular compartment, the haemoglobin and haematocrit levels will fall.

The amount of haemorrhage can be classified into classes 1–4 based on the estimated blood loss required to produce certain physiological compensatory changes (*Table 2.4*). Although conceptually useful, there is variation across ages (the young compensate well, the old very poorly), variation among individuals (e.g. athletes versus the obese) and variation due to confounding factors (e.g. concomitant medications, pain).

Treatment should therefore be based upon the degree of hypovolaemic shock according to vital signs, preload assessment, base deficit and, most importantly, the dynamic response to fluid therapy. Patients who are 'non-responders' or 'transient responders' are still bleeding and must have the site of haemorrhage identified and controlled.

TABLE 2.4 Traditional classification of haemorrhagic shock.

	Class			
	1	2	3	4
Blood volume lost as percentage of total	<15%	15–30%	30–40%	>40%

Management

Identify haemorrhage

External haemorrhage may be obvious, but the diagnosis of concealed haemorrhage may be more difficult. Any shock should be assumed to be hypovolaemic until proven otherwise and, similarly, hypovolaemia should be assumed to be due to haemorrhage until this has been excluded.

Immediate resuscitative manoeuvres

Direct pressure should be placed over the site of external haemorrhage. Airway and breathing should be assessed and controlled as necessary. Large-bore intravenous access should be instituted and blood drawn for cross-matching (see **Cross-matching** below). Emergency blood should be requested if the degree of shock and ongoing haemorrhage warrants this.

Identify the site of haemorrhage

Once haemorrhage has been considered, the site of haemorrhage must be rapidly identified. Note this is not to identify the exact location definitively, but rather to define the next step in haemorrhage control (operation, angioembolisation, endoscopic control).

Clues may be in the history (previous episodes, known aneurysm, non-steroidal therapy for gastrointestinal [GI] bleeding) or examination (nature of blood – fresh, melaena; abdominal tenderness, etc.). For shocked trauma patients, the external signs of injury may suggest internal haemorrhage, but haemorrhage into a body cavity (thorax, abdomen) must be excluded with rapid investigations (chest and pelvis x-ray, abdominal ultrasound or diagnostic peritoneal aspiration).

Investigations for blood loss must be appropriate to the patient's physiological condition. Rapid bedside tests are more appropriate for profound shock and exsanguinating haemorrhage than investigations such as computed tomography (CT) which take time. Patients who are not actively bleeding can have a more methodical, definitive work-up.

Haemorrhage control

The bleeding, shocked patient must be moved rapidly to a place of haemorrhage control. This will usually be in the operating room but may be the angiography or endoscopy suite. These patients require surgical and anaesthetic support and full monitoring and equipment must be available.

Haemorrhage control must be achieved rapidly to prevent the patient entering the triad of coagulopathy–acidosis–hypothermia and physiological exhaustion. There should be no unnecessary investigations or procedures prior to haemorrhage

control to minimise the duration and severity of shock. This includes prolonged attempts to volume resuscitate the patient prior to surgery, which will result in further hypothermia and clotting factor dilution until the bleeding is stopped. Attention should be paid to correction of coagulopathy with blood component therapy to aid surgical haemorrhage control.

Surgical intervention may need to be limited to the minimum necessary to stop bleeding and control sepsis. More definitive repairs can be delayed until the patient is haemodynamically stable and physiologically capable of sustaining the procedure. This concept of tailoring the operation to match the patient's physiology and staged procedures to prevent physiological exhaustion is called 'damage control surgery' – a term borrowed from the military which ensures continued functioning of a damaged ship above conducting complete repairs which would prevent rapid return to battle.

Once haemorrhage is controlled, patients should be aggressively resuscitated, warmed and coagulopathy corrected. Attention should be paid to fluid responsiveness and the end points of resuscitation to ensure that patients are fully resuscitated and to reduce the incidence and severity of organ failure.

Summary box 2.4

Damage control surgery

- Arrest haemorrhage
- Control sepsis
- Protect from further injury
- Nothing else

Damage control resuscitation

These concepts have been combined into a new paradigm for the management of trauma patients with active haemorrhage called damage control resuscitation (DCR). The four central strategies of DCR are:

1 Anticipate and treat acute traumatic coagulopathy.
2 Permissive hypotension until haemorrhage control.
3 Limit crystalloid and colloid infusion to avoid dilutional coagulopathy.
4 Damage control surgery to control haemorrhage and preserve physiology.

Damage control resuscitation strategies have been shown to reduce mortality and morbidity in patients with exsanguinating trauma and may be applicable in other forms of acute haemorrhage.

TRANSFUSION

The transfusion of blood and blood products has become commonplace since the first successful transfusion in 1818. Although the incidence of severe transfusion reactions and infections is now very low, in recent years it has become apparent that there is an immunological price to be paid from the transfusion of heterologous blood, leading to increased morbidity and decreased survival in certain population groups (trauma, malignancy). Supplies are also limited, and therefore the use of blood and blood products must always be judicious and justifiable for clinical need (*Table 2.5*).

TABLE 2.5 History of blood transfusion.

1492	Pope Innocent VIII suffers a stroke and receives a blood transfusion from three 10-year-old boys (paid a ducat each). All three boys died, as did the pope later that year
1665	Richard Lower in Oxford conducts the first successful canine transfusions
1667	Jean-Baptiste Denis reports successful sheep–human transfusions
1678	Animal–human transfusions are banned in France because of the poor results
1818	James Blundell performs the first successful documented human transfusion in a woman suffering post-partum haemorrhage. She received blood from her husband and survived
1901	Karl Landsteiner discovers the ABO system
1914	The Belgian physician Albert Hustin performed the first non-direct transfusion, using sodium citrate as an anticoagulant
1926	The British Red Cross instituted the first blood transfusion service in the world
1939	The Rhesus system was identified and recognised as the major cause of transfusion reactions

Blood and blood products

Blood is collected from donors who have been previously screened before donating, to exclude any donor whose blood may have the potential to harm the patient, or to prevent possible harm that donating a unit of blood may have on the donor. In the UK, up to 450 mL of blood is drawn, a maximum of three times each year. Each unit is tested for evidence of hepatitis B, hepatitis C, HIV-1, HIV-2 and syphilis. Donations are leukodepleted as a precaution against variant Creutzfeldt–Jakob disease (this may also reduce the immunogenicity of the transfusion). The ABO and rhesus D blood groups are determined, as well as the presence of irregular red cell antibodies. The blood is then processed into subcomponents.

Whole blood

Whole blood is now rarely available in civilian practice because it has been seen as an inefficient use of the limited resource. However, whole blood transfusion has significant advantages over packed cells as it is coagulation factor rich and, if fresh, more metabolically active than stored blood.

Hans Gerhard Creutzfeldt, 1885–1946, neurologist, Kiel, Germany.
Alfons Maria Jakob, 1884–1931, neurologist, Hamburg, Germany.
Karl Landsteiner, 1868–1943, Professor of Pathological Anatomy, University of Vienna, Austria. In 1909 he classified the human blood groups into A, B, AB and O. For this he was awarded the Nobel Prize for Physiology or Medicine in 1930.

Packed red cells

Packed red blood cells are spun-down and concentrated packs of red blood cells. Each unit is approximately 330 mL and has a haematocrit of 50–70%. Packed cells are stored in a SAG-M solution (saline–adenine–glucose–mannitol) to increase shelf life to 5 weeks at 2–6°C. (Older storage regimes included storage in CPD: citrate–phosphate–dextrose solutions, which have a shelf life of 2–3 weeks.)

Fresh-frozen plasma

Fresh-frozen plasma (FFP) is rich in coagulation factors and is removed from fresh blood and stored at −40 to −50°C with a 2-year shelf life. It is the first-line therapy in the treatment of coagulopathic haemorrhage (see below under **Management of coagulopathy**). Rhesus D-positive FFP may be given to a rhesus D-negative woman although it is possible for seroconversion to occur with large volumes owing to the presence of red cell fragments, and Rh-D immunisation should be considered.

Cryoprecipitate

Cryoprecipitate is a supernatant precipitate of FFP and is rich in factor VIII and fibrinogen. It is stored at −30°C with a 2-year shelf life. It is given in low fibrinogen states or factor VIII deficiency.

Platelets

Platelets are supplied as a pooled platelet concentrate and contain about 250×10^9/L. Platelets are stored on a special agitator at 20–24°C and have a shelf life of only 5 days. Platelet transfusions are given to patients with thrombocytopenia or with platelet dysfunction who are bleeding or undergoing surgery.

Patients are increasingly presenting on antiplatelet therapy such as aspirin or clopidogrel for reduction of cardiovascular risk. Aspirin therapy rarely poses a problem but control of haemorrhage on the more potent platelet inhibitors can be extremely difficult. Patients on clopidogrel who are actively bleeding and undergoing major surgery may require almost continuous infusion of platelets during the course of the procedure. Arginine vasopressin or its analogues (DDAVP) have also been used in this patient group, although with limited success.

Prothrombin complex concentrates

Prothrombin complex concentrates (PCC) are highly purified concentrates prepared from pooled plasma. They contain factors II, IX and X. Factor VII may be included or produced separately. It is indicated for the emergency reversal of anticoagulant (warfarin) therapy in uncontrolled haemorrhage.

Autologous blood

It is possible for patients undergoing elective surgery to predonate their own blood up to 3 weeks before surgery for retransfusion during the operation. Similarly, during surgery blood can be collected in a cell-saver which washes and collects red blood cells which can then be returned to the patient.

Indications for blood transfusion

Blood transfusions should be avoided if possible, and many previous uses of blood and blood products are now no longer considered appropriate. The indications for blood transfusion are as follows:

- Acute blood loss, to replace circulating volume and maintain oxygen delivery;
- Perioperative anaemia, to ensure adequate oxygen delivery during the perioperative phase;
- Symptomatic chronic anaemia, without haemorrhage or impending surgery.

Transfusion trigger

Historically, patients were transfused to achieve a haemoglobin >10 g/dL. This has now been shown not only to be unnecessary but also to be associated with an increased morbidity and mortality compared with lower target values. A haemoglobin level of 6 g/dL is acceptable in patients who are not actively bleeding, not about to undergo major surgery and are not symptomatic. There is some controversy as to the optimal haemoglobin level in some patient groups, such as those with cardiovascular disease, sepsis and traumatic brain injury. Although, conceptually, a higher haemoglobin level improves oxygen delivery, there is little clinical evidence at this stage to support higher levels in these groups (*Table 2.6*).

TABLE 2.6 Perioperative red blood cell transfusion criteria.

Haemoglobin level (g/dL)	Indications
<6	Probably will benefit from transfusion
6–8	Transfusion unlikely to be of benefit in the absence of bleeding or impending surgery
>8	No indication for transfusion in the absence of other risk factors

Blood groups and cross-matching

Human red cells have on their cell surface many different antigens. Two groups of antigens are of major importance in surgical practice – the ABO and rhesus systems.

ABO system

These proteins are strongly antigenic and are associated with naturally occurring antibodies in the serum. The system consists of three allelic genes – A, B and O – which control synthesis of enzymes that add carbohydrate residues to cell surface glycoproteins. A and B genes add specific residues while the O gene is an amorph and does not transform the glycoprotein. The system allows for six possible genotypes although there are only four phenotypes. Naturally occurring antibodies are found in the serum of those lacking the corresponding antigen (*Table 2.7*).

Blood group O is the universal donor type as it contains no antigens to provoke a reaction. Conversely, group AB individuals are 'universal recipients' and can receive any ABO blood type because they have no circulating antibodies.

TABLE 2.7 ABO blood group system.

Phenotype	Genotype	Antigens	Antibodies	Frequency (%)
O	OO	O	Anti-A, anti-B	46
A	AA or AO	A	Anti-B	42
B	BB or BO	B	Anti-A	9
AB	AB	AB	None	3

Rhesus system

The rhesus D (Rh(D)) antigen is strongly antigenic and is present in approximately 85% of the population in the UK. Antibodies to the D antigen are not naturally present in the serum of the remaining 15% of individuals, but their formation may be stimulated by the transfusion of Rh-positive red cells, or acquired during delivery of a Rh(D)-positive baby.

Acquired antibodies are capable, during pregnancy, of crossing the placenta and, if present in a Rh(D)-negative mother, may cause severe haemolytic anaemia and even death (hydrops fetalis) in a Rh(D)-positive fetus *in utero*. The other minor blood group antigens may be associated with naturally occurring antibodies, or may stimulate the formation of antibodies on relatively rare occasions.

Transfusion reactions

If antibodies present in the recipient's serum are incompatible with the donor's cells, a transfusion reaction will result. This usually takes the form of an acute haemolytic reaction. Severe immune-related transfusion reactions due to ABO incompatibility result in potentially fatal complement-mediated intravascular haemolysis and multiple organ failure. Transfusion reactions from other antigen systems are usually milder and self-limiting.

Febrile transfusion reactions are non-haemolytic and are usually caused by a graft-versus-host response from leukocytes in transfused components. Such reactions are associated with fever, chills or rigors. The blood transfusion should be stopped immediately. This form of transfusion reaction is rare with leukodepleted blood.

Cross-matching

To prevent transfusion reactions, all transfusions are preceded by ABO and rhesus typing of both donor and recipient blood to ensure compatibility. The recipient's serum is then mixed with the donor's cells to confirm ABO compatibility and to test for rhesus and any other blood group antigen–antibody reaction.

Full cross-matching of blood may take up to 45 minutes in most laboratories. In more urgent situations, 'type specific' blood is provided which is only ABO/rhesus matched and can be issued within 10–15 minutes. Where blood must be given emergently, group O (universal donor) blood is given (O– to females, O+ to males).

When blood transfusion is prescribed and blood is administered, it is essential that the correct patient receives the correct transfusion. Two healthcare personnel should check the patient details against the prescription and the label of the donor blood. In addition, the donor blood serial number should also be checked against the issue slip for that patient. Provided these principles are strictly adhered to the number of severe and fatal ABO incompatibility reactions can be minimised.

Complications of blood transfusion

Complications from blood transfusion can be categorised as those arising from a single transfusion and those related to massive transfusion.

Complications from a single transfusion

Complications from a single transfusion include:

- incompatibility haemolytic transfusion reaction;
- febrile transfusion reaction;
- allergic reaction;
- infection:
  - bacterial infection (usually due to faulty storage);
  - hepatitis;
  - HIV;
  - malaria;
- air embolism;
- thrombophlebitis;
- transfusion-related acute lung injury (usually from FFP).

Complications from massive transfusion

Complications from massive transfusion include:

- coagulopathy;
- hypocalcaemia;
- hyperkalaemia;
- hypokalaemia;
- hypothermia.

In addition, patients who receive repeated transfusions over long periods of time (e.g. patients with thalassaemia) may develop iron overload. (Each transfused unit of red blood cells contains approximately 250 mg of elemental iron.)

Management of coagulopathy

Correction of coagulopathy is not necessary if there is no active bleeding and haemorrhage is not anticipated (not due for surgery). However, coagulopathy following or during massive transfusion should be anticipated and managed aggressively. Prevention of dilutional coagulopathy is central to the damage control resuscitation of patients who are actively bleeding.

This is the prime reason for delivering balanced transfusion regimes matching red blood cell packs with plasma and platelets. Based on moderate evidence, when red cells are transfused for active haemorrhage, it is best to match each red cell unit with one unit of FFP and one of platelets (1:1:1). This will reduce the incidence and severity of subsequent dilutional coagulopathy. Crystalloids and colloids should be avoided for the same reason.

The balanced transfusion approach cannot, however, correct coagulopathy. Therefore, coagulation should be monitored routinely, either with point-of-care testing (thromboelastometry) or with laboratory tests (fibrinogen, clotting times). Underlying coagulopathies should be treated in addition to the administration of 1:1:1 balanced transfusions.

There are pharmacological adjuncts to blood component therapy. The antifibrinolytic tranexamic acid is the most commonly administered. It is usually administered empirically to bleeding patients because effective point-of-care tests of fibrinolysis are not yet routinely available. There is little evidence to support the use of other coagulation factor concentrates at this time.

Blood substitutes

Blood substitutes are an attractive alternative to the costly process of donating, checking, storing and administering blood, especially given the immunogenic and potential infectious complications associated with transfusion.

There are several oxygen-carrying blood substitutes under investigation in experimental animal or early clinical trials. Blood substitutes are either biomimetic or abiotic. Biomimetic substitutes mimic the standard oxygen-carrying capacity of the blood and are haemoglobin based. Abiotic substitutes are synthetic oxygen carriers and are currently primarily perfluorocarbon based.

Haemoglobin is seen as the obvious candidate for developing an effective blood substitute. Various engineered molecules are under clinical trials, and are based on human, bovine or recombinant technologies. Second-generation perfluorocarbon emulsions are also showing potential in clinical trials.

FURTHER READING

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