Section I Basic sciences

Chapter 1

General physiology

Kamen Valchanov

Physiology along with anatomy and pharmacology are the foundations of modern medicine. These sciences have evolved dramatically over the last century and it is no longer possible for the ordinary medic to be an expert in the three of these basic sciences and be an expert in their own field too. However, a sound understanding of the basic principles of physiology, anatomy and pharmacology is necessary for safe practice. In the modern world of ultrafast information exchange, data not known by the medical practitioners can easily be acquired by the touch of a button on a smart phone. The smart phone, however, is unlikely to treat a patient, and it is the medic who can make an educated decision on the next course of action. In this chapter we will discuss some of the basic physiology concepts underpinning modern surgical practice. Many of those are referred to in the second section of the book dealing with individual surgical specialties.

Homeostasis

Homeostasis is a property of a system that regulates its internal environment and maintains stable constant conditions. In biological terms, homeostasis refers to maintaining optimal conditions for cell function, i.e. temperature, pH, water and ion content.

A stable pH is important for optimal function of intracellular enzyme systems and all processes to maintain a cell's integrity. Acid–base stability in all cells is achieved with the provision of oxygen, nutrients, and removal of waste products, including CO_2, at an optimal temperature. Maintaining homeostasis is a property of most physiological systems. It can be considered at a cellular level where it is necessary to maintain individual cellular function and cell wall integrity, or it can be considered on a larger scale, concerning the whole organism/body. In the latter, the cardiovascular system regulates blood flow to all tissues, from maintenance of organism blood pressure to local tissue vessel diameter. Respiratory homeostasis maintains gas delivery and waste gas clearance from tissues. And renal and neuroendocrine systems maintain the milieu in which the body functions, namely appropriate energy supply, pH environment, temperature and hydration status.

Osmosis

Osmosis is the spontaneous movement of solvent through a partially permeable membrane into a region of higher solute concentration, in the direction that tends to equalise the solute concentrations on both sides. Osmosis is a concept fundamental to the oncotic

A Surgeon's Guide to Anaesthesia and Peri-operative Care, ed. Jane Sturgess, Justin Davies and Kamen Valchanov. Published by Cambridge University Press.

Table 1.1 Mechanism by which substances move across cell membranes

Process	Summary of action	Common sites of action
Osmosis	Movement of water from an area of low solute concentration to high solute concentration across a semipermeable membrane	All vessels, causes tissue oedema if low intravascular albumin (low solute) concentration
Diffusion	Movement of ions from high concentration to low concentration. It is a slow process and inefficient as it must occur over great distances	All vessels, very important for K^+ which is predominantly intracellular. If plasma K^+ is low, intracellular compartments will mobilise to the plasma compartment – therefore low plasma concentration = VERY low whole body potassium
Filtration	Requires a pressure gradient across the membrane to be traversed. Molecules move from high pressure to low pressure	The kidney, all substances part of the 'ultrafiltrate' in Bowman's capsule. Important amino acids, elements for electrolyte, fluid and acid–base balance etc. are reabsorbed later in the nephron
Active transport	Molecules are transported across membranes regardless of the transmembrane concentration gradient. It is an energy-dependent process	The brain for glucose, amino acids in the kidney (reabsorption), gastric acid in the stomach
Exocytosis	Formation of membrane-enclosed vesicles that move to the cell membrane and discharge their contents. It is energy-dependent	Hormones from the posterior pituitary, pancreatic enzymes, acetylcholine at the neuromuscular junction

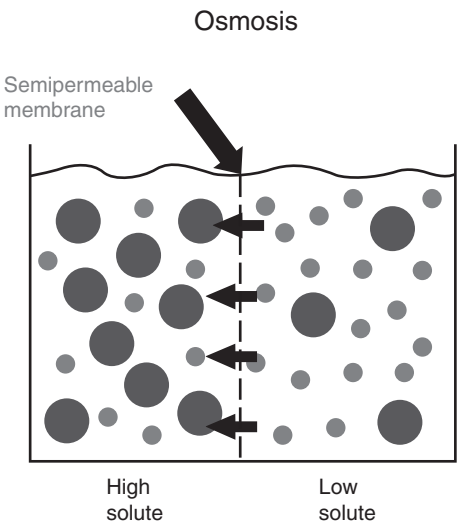

Figure 1.1 Osmosis is the spontaneous movement of solvent through a partially permeable membrane into a region of higher solute concentration.

pressure across the capillary wall (Figure 1.1). The capillary wall acts as a membrane that is impermeable to colloids (plasma proteins, albumin) yet permeable to water. The colloid osmotic pressure owing to the plasma colloids is called oncotic pressure. Water can also be moved across the capillary wall through the mechanism of filtration, i.e. under a pressure difference. In cases where the intravascular colloid (albumin) content is reduced or colloids from the intravascular bed have leaked into the interstitium (e.g. sepsis) the oncotic balance is disrupted, thus drawing water from the vasculature into the extracelluar compartment, producing oedema. It is therefore important that the homeostasis of oncotic pressure is maintained constant in order to avoid oedema.

Thermoregulation

Thermoregulation involves a group of processes that maintain constant optimal temperature for cell function. Humans are homeothermic animals. Tight control of the balance between heat production and loss is essential to maintain normal body functions.

In humans the normal body temperature is considered to be 37 °C, and undergoes circadian fluctuation from 0.5 to 0.7 °C. Temperature regulation is less precise in children. Pregnancy leads to increased basal temperature. This precise balance is regulated by a specialised thermoregulation centre located in the hypothalamus. Disease processes or exercise can lead to impaired thermoregulation and the bodily processes function in different but not normal conditions.

Heat is produced by muscular exercise, assimilation of food and all vital processes of the basal metabolic rate. Many chemical reactions (synthesis and breakdown) lead to a final product/s and heat release. These can be augmented in times of need, by release of hormones (e.g. thyroid, anabolic, catecholamines). Fat is a source of heat that can release heat energy quickly. In particular, brown fat in children can be very efficient.

Heat is lost from the body by radiation, conduction and vaporisation (and evaporation) of water from the respiratory tract and skin. These are discussed in more detail in Chapter 6 Physics and measurement. Radiation and conduction remove 70% of the heat, vaporisation and sweating 27%, respiration 2%, and urination and defaecation 1%.

Fever is of particular interest in medicine. Along with pain it is the commonest and oldest marker of disease. For fever to occur, thermoregulation has to fail, and inflammatory cytokines (pyrogens) produce heat-releasing reactions. An interesting and fortunately rare condition in peri-operative medicine is malignant hyperthermia. It is a result of a mutation in the ryanodine receptor leading to excess release of calcium from muscle. This is triggered by volatile anaesthetic agents or succinylcholine, and if untreated, can be fatal. Prompt recognition and treatment can save lives, and almost always involves cancellation of surgery and post-operative intensive care.

Hypothermia is common in hospitals. It is a result of patients' disease conditions, and their inability to compensate for the increased exposure to low ambient temperature. The multitude of patient exposures for surgery, including patient transfer, air conditioning, application of cold fluids internally and externally and exposed body cavities during surgery may all contribute to hypothermia. Along with reduced metabolic demand, the reduced body temperature results in impaired bodily functions, including cognition, coagulation, immunity and cardio-respiratory function. At temperatures of 32 °C and below, the heart develops arrhythmias and asystole may ensue. The National Institute for Health and Clinical Excellence (NICE) produced guideline 65 in 2008 to prevent inadvertent

peri-operative hypothermia in adults. Many warming blankets and other devices are now available to help prevent inadvertent peri-operative hypothermia.

Metabolic pathways

Precise balance between energy production and consumption in the body is essential. Hormones regulate the metabolic processes producing energy and heat (thermal energy). They also regulate the energy-consuming processes. The first law of thermodynamics states that energy is neither created nor destroyed; it merely changes its form. As such there must be a balance between caloric intake and energy output. The imbalance leads to obesity or starvation.

The energy metabolism consists of basal metabolic rate plus the metabolism for additional functions. The basal metabolic rate is the energy required for support of all basic functions and maintenance of cell wall integrity, which cannot be switched off. This is traditionally the metabolic rate during sleep in a room at comfortable temperature. Any additional activity, such as exercise, stress, surgery or intensive intellectual processes, requires additional energy.

At a cellular level the energy storage is in the form of high-energy phosphate compounds, mostly adenosine triphosphate (ATP) in the mitochondria. Upon aerobic hydrolysis to adenosine diphosphate (ADP) there is a release of energy required for muscle contraction, active transport and synthesis. Further hydrolysis to adenosine monophosphate (AMP) releases more energy. Another energy-rich phosphate is the muscle creatine phosphate.

During exercise, the energy demand increases over the basal metabolic rate and additional ATP energy release is required. A similar condition occurs in patients undergoing surgery. Because of the stress induced by surgery, an array of metabotropic hormones are released, all metabolic processes are augmented, inflammatory mediators released, heat is lost, the heart rate increases and glycogen is released from the liver. Additional utilisation of oxygen is required, and additional CO_2 is produced. This explains why patients with critically impaired cardio-respiratory function can live comfortably at home with few symptoms, whereas they can rapidly deteriorate or die as a result of even minor surgical stress (Figure 1.2).

Carbohydrate metabolism

Carbohydrates are an important dietary source of energy. The commonly ingested carbohydrates are hexoses (glucose, galactose, fructose). These are quickly converted to glucose in the circulation after ingestion. The glucose is then distributed and absorbed by most tissues by the action of molecules called glucose transporters. These facilitate diffusion by concentration gradients. Only gut and kidneys take up glucose by energy-dependent active transport. Once the glucose enters the cells it undergoes transformation to glucose-6-phosphate. The glucose-6-phosphate is either converted into glycogen in the liver (glycogenesis), or broken down (glycolysis) to produce energy. The liver glycogen serves as an energy store (of carbohydrate). On the other hand the glycolysis, through several enzymatic breakdowns, produces pyruvate, which is used in the citric acid cycle in the mitochondria, thereby generating ATP (Figure 1.3). Some of the pyruvate is converted to lactate (catalysed by NADH) in the absence of oxygen. When the oxygen supply is restored the accumulated lactate is converted back to pyruvate.

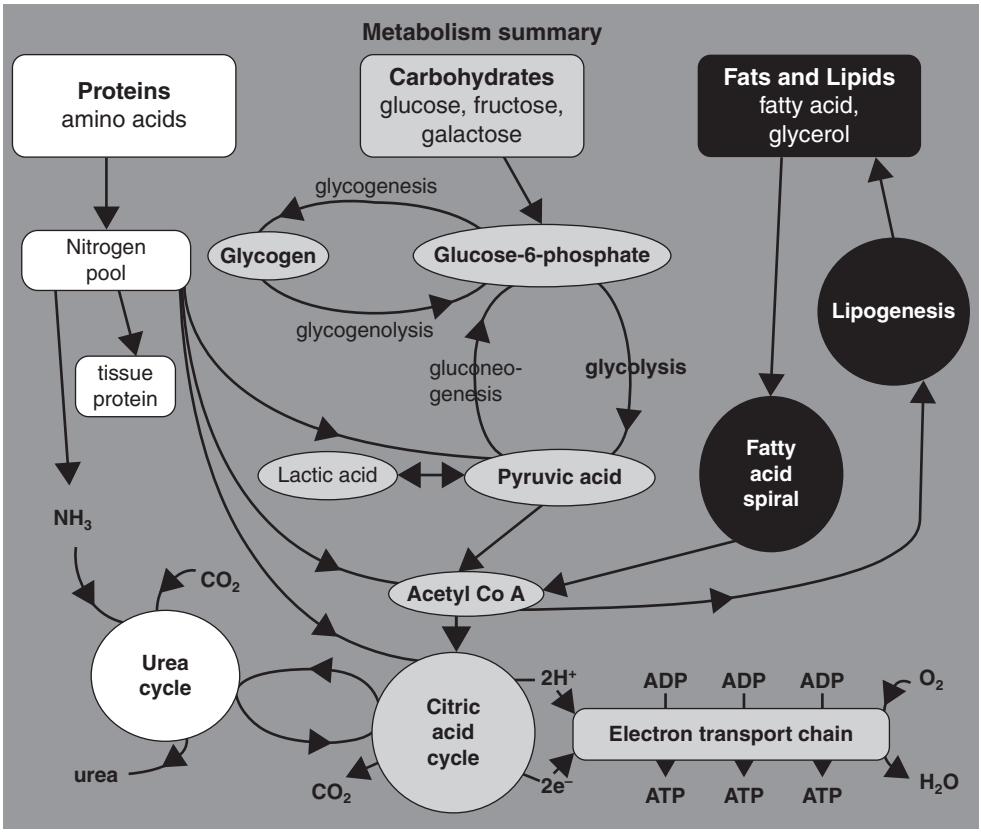

Figure 1.2 Metabolism summary. The main energy source in the body is carbohydrate aerobic breakdown. In addition to this, the fatty acid breakdown can also produce acetyl Co A for the citric cycle, feeding electrons for ATP production, but this pathway is less generous in its supply and only used as a secondary pathway. Finally, the protein breakdown can also be used for energy production but is least efficient.

These processes are hormonally regulated. The main player is insulin. Insulin enhances tissue take up of glucose from the circulation and increases glycogen storage. It also regulates the aerobic glucose breakdown to the citric acid cycle. The deficiency of insulin conversely causes glycogen breakdown and glucose release in the circulation. Glucagon has the opposite effects, forcing glycogenolysis. Similar actions are produced by cortisol and adrenaline. In a clinical situation like septic shock, or after the stress of major surgery, augmented release of adrenaline and cortisol and relative deficiency of insulin impair glucose metabolism. The patient presents with hyperglycaemia and lactic acidosis (as a result of hypoperfusion of tissues and anaerobic carbohydrate metabolism and liver dysfunction with reduced lactic metabolism).

The highly efficient energy release of triphosphate resynthesis is an oxygen-demanding process (aerobic). However, under special circumstances, when there is an oxygen debt, anaerobic (oxygen independent) pathways release energy through carbohydrate breakdown to lactic acid (e.g. during excessive exercise, or tissue hypoxia from pathological causes). During exercise the anaerobic pathways are self-limiting because of build up of lactic acid and decline of pH. On the other hand the body cannot easily compensate for iatrogenic

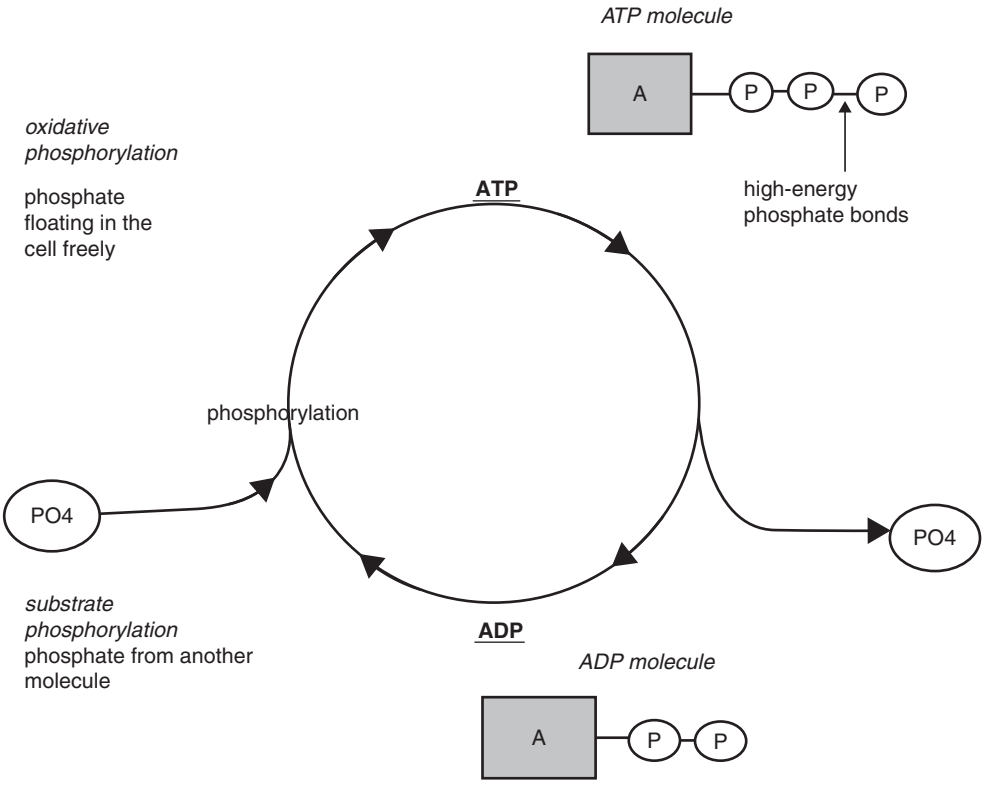

Figure 1.3 ATP synthesis and breakdown is achieved through phosphorylation and dephosphorylation of the adenosine molecule.

anaerobic conditions. For example after application of limb tourniquets or aortic cross clamp there is a substantial lactic acid build up in the distal tissues, which is released into the circulation once the tourniquets or clamp are released, resulting in acidosis and increased respiratory rate. The second insult to the cardiovascular system is the return of cold blood with an elevated potassium concentration. This ischaemic time needs to be limited for two reasons: to avoid tissue necrosis, and to preclude overwhelming acidosis on reperfusion. Similar effects are seen when reperfusing donated organs with prolonged cold ischaemic times, and cardiac arrest has occurred in the recipient. This is often quickly resolved with simple measures and CPR, but can result in death.

Arterial blood gas analysis

Arterial blood gas analysis is one of the most useful monitoring tools in modern medicine. It provides information about pH, oxygen and CO_2 tension, and allows a number of calculated values, including HCO_3^- and base excess. The importance of these will be discussed below.

The pH is a crucial number defining acid–base balance. It represents the balance between all bases and acids and hence the metabolic milieu of the cellular metabolism. The pH is defined as a negative logarithm to the base of 10 of the hydrogen ion concentration, and its normal value is 7.4 (equivalent to 40 pmol/l H^+). The value is a scalar; it has no measurement unit, it is a mere number. Interestingly, H^+ concentrations are expressed in $\times.10^{-8}$ – $\times.10^{-7}$ mmol/l, which are challenging to calculate. In 1909, the Danish chemist Sorensen introduced the pH as a tool for simplifying these long numbers in his PhD, and it is still used by the rest of the world now.

A pH more than 7.44 is called alkalosis, and less than 7.36 acidosis. The acid–base balance is governed by respiratory and metabolic function. The respiratory function can affect it by maintaining the blood CO_2 tension. Therefore, hypercarbia (pCO_2 greater than 6 kPa) causes respiratory acidosis. The respiratory acidosis is compensated if pH remains normal (7.36 –7.44), and this can be achieved by metabolic compensation, i.e. increasing HCO_3 concentration. Conversely, hypocarbia (pCO_2 lower than 4.5 kPa) causes respiratory alkalosis. The respiratory alkalosis can be compensated if the pH remains normal, and this can be achieved by metabolic compensation, i.e. reducing HCO_3 concentrations. The metabolic pathways of regulating acid–base status involve blood buffering and renal excretion of solutes, but revolve around the HCO_3 concentration in the blood. Metabolic acidosis is caused by low HCO_3 concentrations (less than 21 mmol/l) and can be compensated if the pH is normal and there is a respiratory compensation by hypocarbia. Conversely, metabolic alkalosis is represented by high HCO_3 concentrations (greater than 26 mmol/l), and can be respiratory compensated by hypercarbia. The best way of making sense of this is by analysis using a Davenport diagram (Figure 1.4).

The easiest way of analysing arterial blood gases is by using only three variables (pH, pCO_2 and HCO_3). If the pH is less than 7.4 then the primary problem is likely to be acidosis, compensated or uncompensated. A typical example of compensated metabolic acidosis is: pH 7.38, pCO_2 4.4 kPa, and HCO_3 19 mmol/l. If the pH is more than 7.4 then the primary problem is likely to be alkalosis. A typical example of decompensated metabolic alkalosis is pH 7.5 pCO_2 6.5 kPa, and HCO_3 31 mmol/l.

Normal arterial blood gas values are:

	Low	High
pH	7.36	7.44
pCO_2	4.6 kPa	6 kPa
pO_2	10 kPa	13 kPA
HCO_3	21 mmol/l	26 mmol/l
Sats	95%	100%
BE	-2.5 mmol/l	+2.5 mmol/l

Another calculated value in the arterial blood gas analysis is base excess. Base excess is a fictitious value as it does not exist in real life, and yet it governs so much decision-making in UK intensive care units. It is defined as the amount of acid which needs to be added to a solution to reduce the pH to 7.4. Conversely, the base deficit is the amount of base that needs to be added to a solution to increase the pH to 7.4. During cardiopulmonary bypass

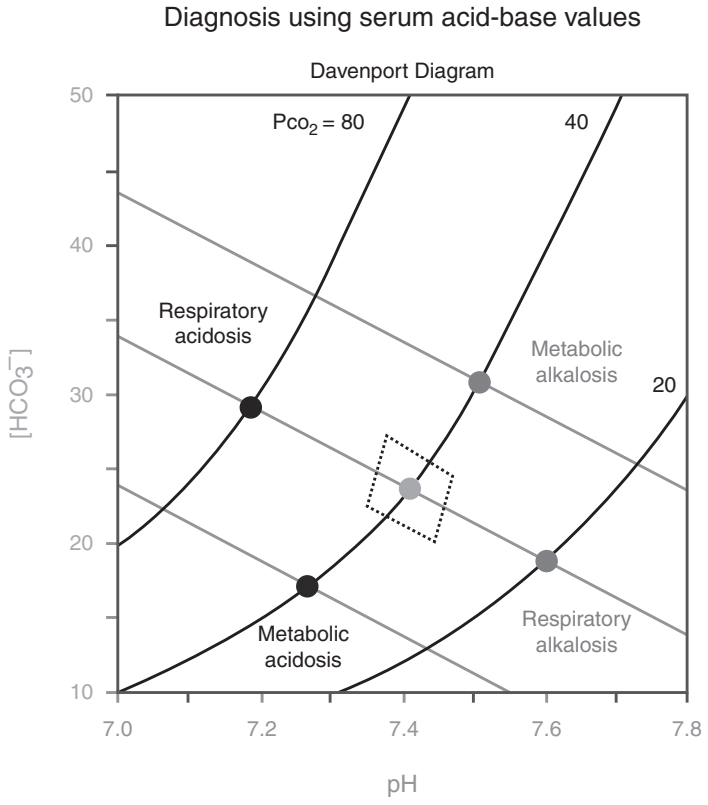

Figure 1.4 Davenport diagram.

when the base excess is less than -5, i.e. there is base deficit, the perfusionists would normally add HCO_3 to treat the number. On the other hand the same number in most UK intensive care units will be left untreated, and in fact adding $NaHCO_3$ is frowned upon. It is not known if treating base deficit by the addition of $NaHCO_3$ worsens prognosis, but it does not address the primary question, i.e. the reason for acidosis.

Sepsis and septic shock

Sepsis is a clinical syndrome characterised by a multisystem response to a microbial pathogenic insult consisting of a mosaic of interconnected biochemical, cellular, and organ–organ interactions. The Surviving Sepsis campaign defines it also as:

> 'Presence of inflammation together with systemic manifestations of infection.'

Severe sepsis is defined as:

> 'Sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion.'

Septic shock is defined as:

> 'Sepsis-induced tissue hypoperfusion persisting despite adequate fluid resuscitation.'

Table 1.2 Diagnostic criteria for sepsis: infection, documented or suspected, and some of the following:

General variables	Fever (> 38.3 °C) Hypothermia (core temperature < 36 °C) Heart rate > 90/min – one or more than two SD above the normal value for age Tachypnoea Altered mental status Significant oedema or positive fluid balance (> 20 mL/kg over 24 hrs) Hyperglycaemia (plasma glucose > 140 mg/dL or 7.7 mmol/l) in the absence of diabetes
Inflammatory variables	Leukocytosis (WBC count > 12,000 μl^{-1}) Leukopenia (WBC count < 4000 μl^{-1}) Normal WBC count with greater than 10% immature forms Plasma C-reactive protein more than two SD above the normal value Plasma procalcitonin more than two SD above the normal value
Haemodynamic variables	Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or a SBP decrease > 40 mm Hg in adults or less than two SD below normal for age)
Organ dysfunction variables	Arterial hypoxaemia (Pao_2/Fio_2 < 300) Acute oliguria (urine output < 0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation) Creatinine increase > 0.5 mg/dL or 44.2 µmol/l Coagulation abnormalities (INR > 1.5 or aPTT > 60 s) Ileus (absent bowel sounds) Thrombocytopenia (platelet count < 100,000 μl^{-1}) Hyperbilirubinaemia (plasma total bilirubin > 4 mg/dl or 70 µmol/l)
Tissue perfusion variables	Hyperlactataemia (> 1 mmol/l) Decreased capillary refill or mottling

Another term used in sepsis literature is SIRS (systemic inflammatory response syndrome): the diagnosis requires four derangements –

1. Temperature < 36 °C or >38 °C
2. Heart rate > 90 bpm
3. Respiratory rate > 20 bpm (or PCO_2 < 4.3 kPa)
4. White blood cells < 4.10^9/l or > 10.10^9/l

Systemic inflammatory response syndrome is a syndrome which reflects the generalised body reaction to an insult. While it is a reliable feature of the septic process there are conditions resembling sepsis by definition and fulfilling the SIRS criteria. A typical condition is pancreatitis where, owing to autolysis and release of digestive hormones in the circulation, a sterile inflammatory cascade produces a generalised septic response.

The general diagnostic criteria for sepsis are summarised in Table 1.2. This is a condition that requires prompt treatment. The simplified recommendations for the treatment include:

A. Initial resuscitation: with volume against a haemodynamic target;
B. Diagnosis: septic screen and imaging for potential source of infection;

C. Antimicrobial therapy;
D. Source control: where source is found, targeted treatment including surgery to be considered early.

Fluid balance and replacement

The human body relies on a well-balanced intravascular volume to maintain optimal circulation for different circumstances. This in turn ensures sufficient oxygen tissue supply and CO_2 clearance. The circulating blood volume is tightly regulated by neural, hormonal and renal systems. Additionally, blood is regulated in its haemoglobin content, osmolality and solute concentrations.

Cardiac output is governed by cardiac pump function, peripheral vascular resistance and circulating blood volume. These factors also interact with lung function. Cardiac output itself depends on pre-load, heart rate, myocardial contractility and afterload.

Pre-load is largely represented by the total circulating blood volume. Afterload is represented by the peripheral vascular resistance and, to a lesser extent, circulating blood volume. These parameters are frequently altered in the peri-operative period. The circulating blood volume can be diminished (owing to blood loss) or redistributed (owing to reduction of peripheral vascular resistance or plasma volume sequestration in abdominal organs). Maintaining a physiological state of the body fluid compartments as far as possible would mean a careful and adequate substitution of actual fluid losses. There are two types: fluid losses through urine, digestive tract and insensible losses; surgery-related fluid losses, i.e. pre-operative dehydration, bleeding and fluid redistribution.

When choosing fluid replacement regimes in the peri-operative setting two facts need to be born in mind:

1. The extracellular deficit after usual fasting is low;
2. The basal fluid loss via insensible perspiration is approximately 0.5 ml/kg/h, extending to 1 ml/kg/h during major abdominal surgery.

Therefore volume loading in pre-operatively euvolaemic patients is not necessary. In fact overhydration can lead to oedema, slow recovery, and potentially lead to peri-operative complications and higher mortality. Fluid use should be targeted at replacing lost volume only.

Colloids and crystalloids

Volume replacement in the peri-operative period could be achieved by either crystalloid or colloid solutions. Colloids are solutions containing substances that are evenly dispersed throughout. Crystalloids are solutions containing substances that can pass through a semipermeable membrane. All have advantages and disadvantages, as discussed below. Over the last half century, scientists have been trying to develop blood substitutes with oxygen-carrying capacity in addition to volume expansion properties. Fluorocarbons and synthetic haemoglobins have been studied, but none are currently in clinical use. Please see Chapter 24 'Fluids' for further information.

Crystalloid solutions

Normal saline (0.9% NaCl): Contains 154 mmol/l Na^+ and 154 mmol/l Cl^-, pH 5.0. It stays in the circulation for a short time (30–60 minutes), and can produce oedema when it exits the vascular bed. It can also cause hyperchloraemic metabolic acidosis.