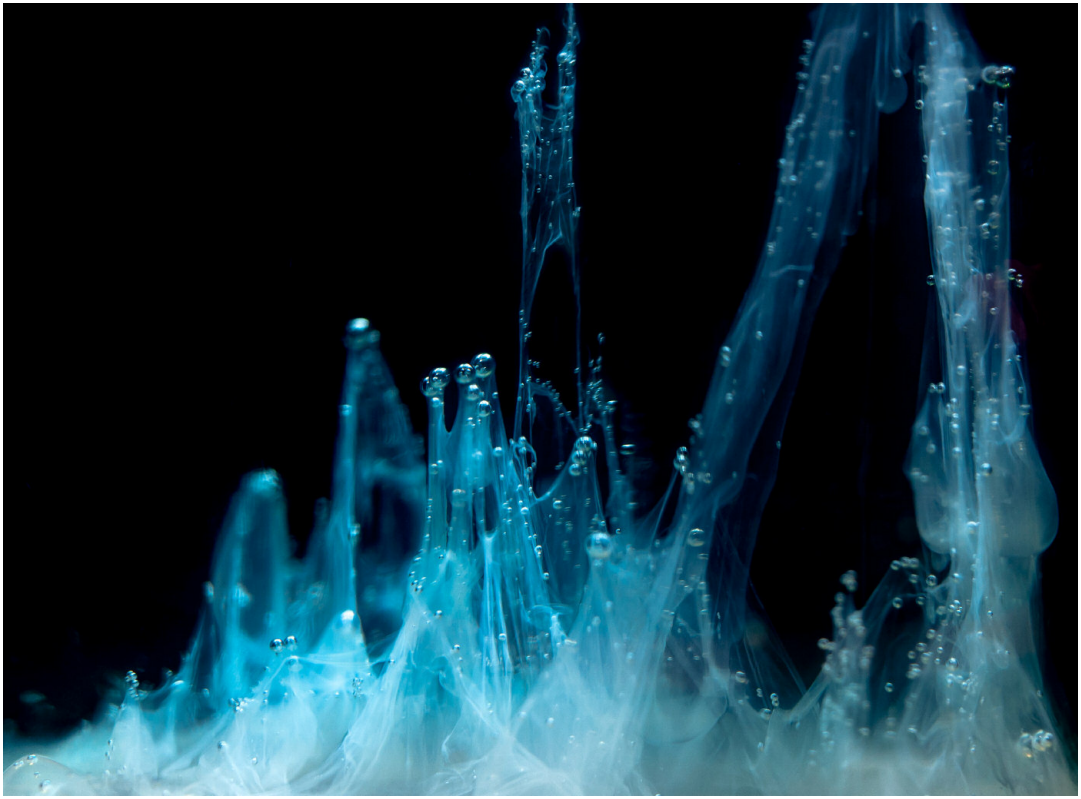

Dileep N. Lobo
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Simon P. Allison

BASIC CONCEPTS OF FLUID AND ELECTROLYTE THERAPY

2nd Edition

The authors have made every effort to ensure that drug dosages in this book are in accordance with current recommendations and practice at the time of publication.
However, the reader is urged to check the package insert for each drug for any changes in indications and dosage and for added warnings and precautions.

The publication of this book was supported by an unrestricted educational grant from B.Braun Melsungen AG. B. Braun did not have a role in deciding the content of the book.

BASIC CONCEPTS OF FLUID AND ELECTROLYTE THERAPY

2nd Edition

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PREFACE

The first edition of this book was published in 2013 with the aim of improving understanding and clinical practice in the field of fluid and electrolyte therapy. Studies at that time suggested that, even though fluid and electrolyte preparations are the most commonly prescribed medications in hospitals, management of fluid and electrolyte disorders was suboptimal, possibly due to inadequate teaching, causing avoidable morbidity and even mortality. It should not be forgotten that fluid therapy, like other forms of treatment, has the capacity to do harm as well as good unless administered with care and based on sound knowledge.

A second edition was felt appropriate in the light of further advances in knowledge and practice over the last 9 years. We have updated the book, adding new chapters, figures, tables and flow charts to help the reader. New chapters include Ageing and Fluid Balance, Chronic Kidney Disease, Fluid Overload and the De-escalation Phase, and Perioperative Fluid Therapy and Outcomes. We have also tried to maintain consistency with published national and international guidelines, where available. References have now been cited in the text. To limit the number of references, we have tried, as far as possible to cite impor-tant review articles from which original studies may be sourced. However, relevant original works have been referred to when appropriate. We have included multiple choice questions so that readers may test their knowledge after reading the book.

The subject of fluid balance in paediatrics is not addressed and this book should be regarded as relevant to adults only. It is still not our intention to write a comprehensive textbook dealing with complex problems, but to provide a basic hand-book for students, nurses, trainee doctors and other health care professionals to help them to understand and solve some of the most common practical problems they face in day to day hospital practice. We hope that it will also stimulate them to pursue the subject in greater detail with further reading and practical experience. In difficult cases, or where there is uncertainty, trainee health care professionals should never hesitate to ask for advice from senior and experienced colleagues.

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Simon P. Allison

List of Abbreviations

ACE	angiotensin converting enzyme
ACEi	angiotensin converting enzyme inhibitor
ACR	albumin creatinine ratio
ADH	antidiuretic hormone
AKD	acute kidney disease
AKI	acute kidney injury
ANA	anti-nuclear antibody
ANCA	antineutrophil cytoplasmic antibody
ARB	angiotensin receptor blocker
ATN	acute tubular necrosis
BD	base deficit
BE	base excess
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CVP	central venous pressure
CXR	chest X-ray
DKA	diabetic ketoacidosis
ECF	extracellular fluid
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ERAS	enhanced recovery after surgery
FBC	full blood count
GDFT	goal directed fluid therapy
GFR	glomerular filtration rate
GI	gastrointestinal
Hct	haematocrit
HES	hydroxyethyl starch
HONK	hyperosmolar non-ketotic
ICF	intracellular fluid
ISS	interstitial space
IVS	intravascular space
JVP	jugular venous pressure
KDIGO	kidney disease improving global outcomes
LFTs	liver function tests
MDRD	Modification of Diet in Renal Disease
NHS	National Health Service (UK)
NICE	National Institute for Health and Care Excellence (UK)
NSAIDs	non-steroidal anti-inflammatory drugs
RAAS	renin angiotensin aldosterone system
RTA	renal tubular acidosis
RRT	renal replacement therapy
SCr	serum creatinine
SIADH	syndrome of inappropriate ADH secretion
SID	strong ion difference
STAT-3	signal transducer and activation of transcription-3
TBW	total body water
U&Es	urea and electrolytes
USS	ultrasound scan
VRII	variable rate insulin infusion

Chapter 1:
NORMAL ANATOMY AND PHYSIOLOGY OF THE BODY FLUIDS

INTRODUCTION

When primitive marine unicellular organisms evolved into multicellular forms and emerged onto land, they faced several physiological challenges including the maintenance of water and salt balance in an environment low in both. Rather than being surrounded by an external sea, they carried with them their own internal sea or extracellular fluid (ECF), in which their cells could bathe in a constant chemical environment, which the great French physiologist Claude Bernard called the '*milieu interieur*'[1,2]. In this environment the cells retain their energy consuming and primeval capacity to pump sodium out and to retain potassium to neutralise the negative charges of proteins and other ions.

While fluid balance is usually considered as that between the body and its environment, i.e. external balance, disease also affects the internal balance between the various body fluid compartments, e.g. between the intravascular and interstitial components of the ECF, between the intracellular fluid (ICF) and the ECF, and between the ECF and the gut and other internal spaces[3,4].

NORMAL ANATOMY AND PHYSIOLOGY

Water comprises about 60% of the body weight of an average adult, although the percentage is lower in those with obesity, since adipose tissue contains less water than lean tissue[5]. As shown in **Figs. 1.1 and 1.2**, the total body water is divided functionally into the extracellular and the intracellular fluid spaces (ECF≈20% body weight and ICF≈40% body weight) separated by the cell membrane with its active sodium pump, which ensures that sodium remains largely in the ECF. The cell, however, contains large anions such as protein and glycogen, which cannot escape and, therefore, draw in potassium ions to maintain electrical neutrality (Gibbs-Donnan equilibrium[6]). These mechanisms ensure that sodium and its balancing anions, chloride and bicarbonate, are the mainstay of ECF osmolality, and potassium has the corresponding function in the ICF (**Table 1.1**).

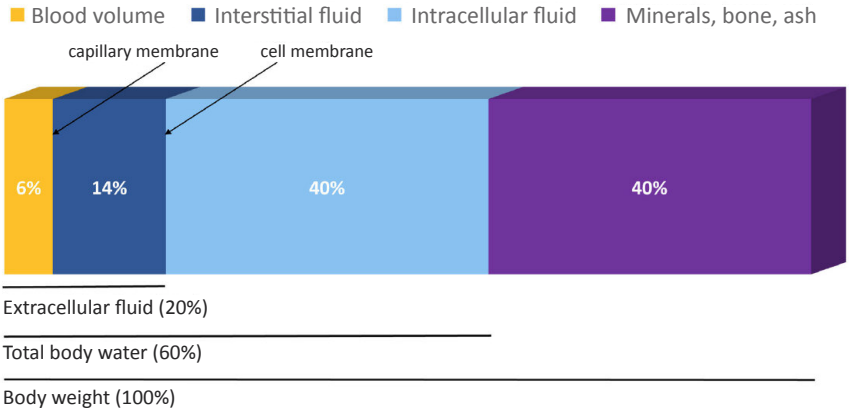

Fig. 1.1: Body fluid compartments as approximate percentages of body weight. Red blood cells (haematocrit) account for approximately 40-45% of total blood volume, the rest being plasma.

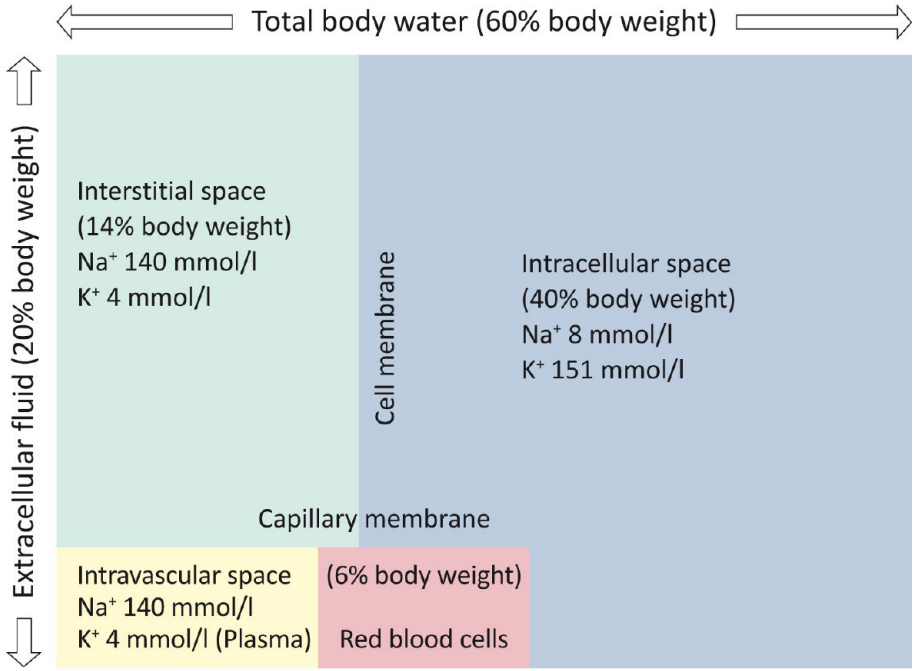

Fig. 1.2: Body fluid compartments with approximate electrolyte concentrations. Red blood cells (haematocrit) account for approximately 45% of total intravascular volume.

Table 1.1: Body fluid compartments with approximate electrolyte concentrations.

Electrolyte	ECF (mmol/L)	ICF (mmol/L)	Total in body (mmol)
Sodium	140-145	10-18	3000-4000
Potassium	3.5-5.5	120-145	3000-4000
Calcium	2.2-2.5		25000-27000
Ionised calcium	0.9-1.3		
Magnesium	0.7-1.2	15-25	900-1200
Chloride	98-106	2-6	3000-4000
Phosphate	0.7-1.3	8-20	30000-32000

The ECF is further divided into the intravascular (within the circulation) and the interstitial (extravascular fluid surrounding the cells) fluid spaces. The intravascular space (blood volume ≈6-7% of body weight) has its own intracellular component in the form of red (haematocrit ≈40-45%) and white cells and an extracellular element in the form of plasma (≈55-60% of total blood volume).

The intravascular and extravascular components of the ECF are separated by the capillary membrane, with its micropores, which allow only a slow escape rate of albumin (5%/h)[7], which is then returned to the circulation via the lymphatics at the same rate, thereby maintaining equilibrium (**Fig. 1.3**). While the hydrostatic pressure within the circulation tends to drive fluid out, the oncotic pressure of the plasma proteins, e.g. albumin, draws fluid in and maintains the relative constancy of the plasma volume as a proportion of the ECF (Starling effect)[8].

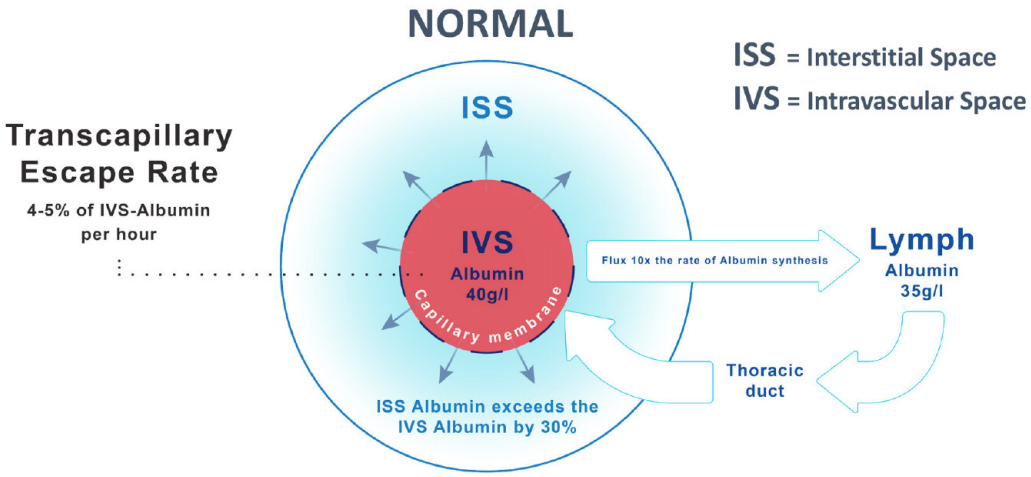

Fig. 1.3: Transcapillary escape of albumin in health.

There is also a clinically important flux of fluid and electrolytes between the ECF and the gastrointestinal (GI) tract involving active secretion and reabsorption of digestive juices (**Fig. 1.4**). In health there is a constant flux between these various spaces and important physiological mechanisms ensure a constant relationship between them, which we may term the internal fluid balance[3,4].

The external fluid and electrolyte balance between the body and its environment is defined by the intake of fluid and electrolytes versus the output from the kidneys, the gastrointestinal tract, and the skin and lungs (insensible loss). Since the external and internal balances may be disturbed by disease, it is important to understand normal physiology in order to appreciate the disorders, which may occur in patients.

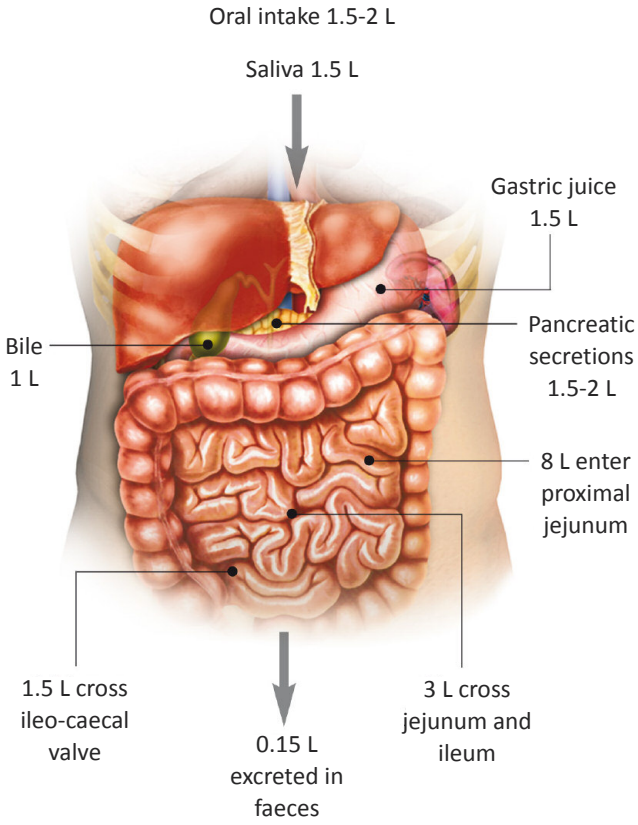

Fig. 1.4: Flux of fluid across the gastrointestinal tract.

External balance

Values for the normal daily intake and output of fluid and electrolytes are shown in **Tables 1.2 and 1.3**. These are only an approximate guide and may have to be modified in the presence of excessive losses, e.g. of water and salt through increased sweating and insensible loss in hot climates. They may also need to be modified in the presence of disease, e.g. gastroenteritis, which causes abnormal losses of fluid and electrolyte from the gastrointestinal tract (**Fig. 1.3** and **Table 1.4**).

Table 1.2: Approximate daily water balance in health.

Intake (ml)		**Output (ml)**	
Water from beverages	1200	Urine	1500
Water from solid food	1000	Insensible losses from skin and lungs	900
Metabolic water from oxidation	300	Faeces	100

Table 1.3: Normal maintenance requirements for water and electrolytes.

Water	25-30 ml/kg/day
Sodium	0.9-1.2 mmol/kg/day
Potassium	1 mmol/kg/day

Table 1.4: Approximate electrolyte content of gastrointestinal secretions and sweat.

Secretion	Na^+ (mmol/L)	K^+ (mmol/L)	Cl^- (mmol/L)
Saliva	40	20	40
Gastric juice	70-120	10	100
Bile	140	5	100
Pancreatic juice*	140	5	75
Small intestine	110-120	5-10	105
Diarrhoea (adult)	120	15	90
Sweat	30-70	0-5	30-70

*Pancreatic juice has a bicarbonate content of 50-70 mmol/l

Intake

Under normal circumstances most of our fluid intake is oral, but remember that all food contains some water and electrolytes and that water and carbon dioxide are end products of the oxidation of foodstuffs to produce energy. This metabolic water makes a small but significant contribution to net intake. Our drinking behaviour is governed by the sensation of thirst, which is triggered whenever our water balance is negative through insufficient intake or increased loss. It may also be triggered by a high salt intake, which necessitates the drinking and retention of extra water to maintain the ECF sodium concentration and osmolality in the normal range.

Although it may be blunted in the elderly, in most people the thirst mechanism ensures that intake matches the needs of bodily functions, maintaining a zero balance in which intake and output are equal and physiological osmolality of plasma (280-290 mOsm/kg) is maintained.

More than a century ago Claude Bernard coined the term 'volume obligatoire'[1,2] to describe the minimum volume of urine needed to excrete waste products, such as urea, in order to prevent them accumulating in the blood. This concept implies that, if sufficient fluid has been drunk or administered to balance insensible or other losses and to meet the needs of the kidney, there is no advantage in giving additional or excessive volumes. Indeed, excessive intakes of fluid and electrolytes may be hazardous under certain circumstances (see below) and overwhelm the capacity of the kidney to excrete the excess and maintain normal balance. Salt and water retention causes oedema, which only becomes clinically apparent when the ECF has been expanded by at least 2.5-3 litres[9].

Output

- Insensible loss: evaporation of water from the lungs and skin occurs all the time without us being aware of it. In temperate climates the amount so lost is 500-1000 ml/day. This may be even greater in a warm environment, during fever, or with exertion, when we produce additional sweat containing up to 50 mmol/L of sodium (and chloride). Patients with extensive burns can also have abnormally high insensible losses from the damaged tissues.
- Gastrointestinal losses: normally, the intestine absorbs water and electrolytes very efficiently so that fluid loss in the stool is as little as 100-150 ml/day, although, in the presence of disease this may be increased (**Table 1.4** and **Fig. 1.3**).
- Kidney: this is the main organ for regulating fluid and electrolyte balance as well as excreting the waste products of metabolism, such as urea and creatinine. In this function, its activity is controlled by pressure and osmotic sensors and the resulting changes in the secretion of hormones. The modest daily fluctuations in water and salt intake cause small changes in plasma osmolality and volume which trigger both osmoreceptors and baroreceptors. This, in turn, causes changes in thirst sensation and also in renal excretion of water (via antidiuretic hormone) and salt (via aldosterone). If blood or ECF volumes are threatened by abnormal losses, baroreceptors are triggered (see below) and override the osmoreceptors. In the presence of large volume changes, therefore, the kidney is less able to adjust osmolality, which can be important in some clinical situations (**Fig. 1.5**).

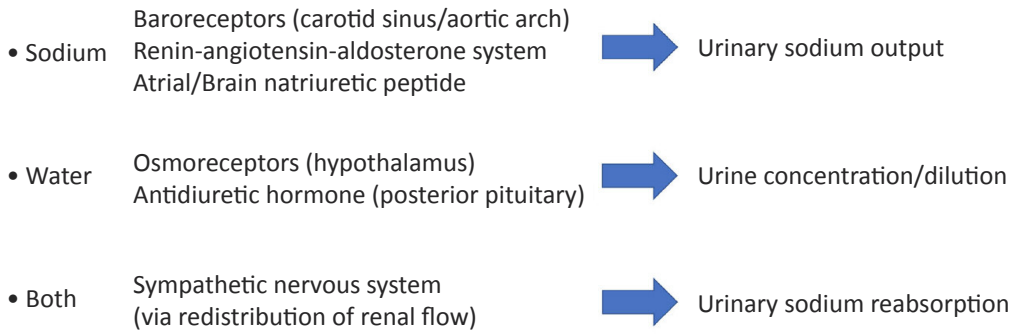

Fig. 1.5: Pathways for response to changes in water and sodium in the extracellular fluid.

- Water:
  Organs, which sense the changes in osmolality of plasma (osmoreceptors), are located in the hypothalamus and signal the posterior pituitary gland to increase or decrease its secretion of vasopressin or antidiuretic hormone (ADH). Dilution of the ECF, including plasma, by intake of water or hypotonic fluid, causes ADH secretion to fall, so that the distal tubules of the kidney excrete more water and produce a dilute urine (this dilution requires the permissive effect of glucocorticoid upon the distal tubules and is, therefore, lost in adrenal insufficiency – one of the reasons for the hyponatraemia of Addison's disease). Conversely, dehydration causes the ECF to become more concentrated. ADH

secretion then rises and the renal tubules reabsorb more water, producing a concentrated urine. In response to dehydration, the normal kidney can concentrate urea in the urine up to a hundred-fold, so that the normal daily production of urea during protein metabolism can be excreted in as little as 500 ml of urine (volume obligatoire).

In the presence of dehydration, the urine to plasma urea or osmolality ratio is, therefore, a measure of the concentrating capacity of the kidney[10]. Age and disease can impair this function so that a larger volume of urine is required to excrete the same amount of waste products. Also, in the presence of a high protein intake or of increased protein catabolism, a larger volume of urine is needed to clear the resulting increase in urea production.

To assess renal function, therefore, measurement of both urinary volume and concentration (osmolality) are important, and the underlying metabolic circumstances should be taken into account. If serum urea and creatinine concentrations remain normal and unchanged over 24 hours, then fluid intake has been adequate, and the urinary 'volume obligatoire' has been achieved.

- Sodium (Na^+)
  Since the integrity of the ECF volume and its proportion of the total body water are largely dependent on the osmotic effect of sodium and its accompanying anions (e.g. Cl^-, HCO_3^-), it is important that the kidneys maintain sodium balance within narrow limits. If salt depletion occurs, then the ECF, and with it the plasma volume falls. Pressure sensors in the circulation are then stimulated and these cause renin secretion by the kidney. This, in turn, stimulates aldosterone secretion by the adrenal gland, which acts on the renal tubules, causing them to reabsorb and conserve sodium. Under normal conditions, therefore, the urinary sodium excretion reflects underlying sodium balance. In the presence of disease, however, this relationship breaks down and reliance on urinary sodium measurements can give rise to errors in treatment (see below and **Chapter 14**).

  Conversely, if the intake of sodium is excessive, the renin-angiotensin-aldosterone system (RAAS) switches off, allowing more sodium to be excreted until normal balance is restored. The mechanism for salt conservation is extremely efficient and the kidney can reduce the concentration of sodium in the urine to <5 mmol/L. On the other hand, even in health, we are slow to excrete an excess salt load, possibly because our physiology has evolved in the context of a low salt environment and has not until modern times been exposed to excessive salt intake. The response of atrial natriuretic peptide to fluid infusions seems to be related more to volume (stretching of the right atrium) than sodium load *per se*[11].

  The mechanism for maintaining sodium balance may become disturbed in disease, leading to sodium deficiency or, more commonly, to excessive sodium retention, with consequent oedema and adverse clinical outcome (see **Chapter 16**).

- Potassium (K^+)
  Although only a small proportion of the body's potassium is in the extracellular space, its concentration has to be maintained within narrow limits (3.5-5.3 mmol/L) to avoid the risk of muscular dysfunction or potentially fatal cardiac events. This is achieved by exchange of potassium in the renal tubules for Na^+ or H^+, allowing more or less potassium to be excreted. In the presence of potassium deficiency, H^+ ion reabsorption is impaired, leading to hypokalaemic alkalosis.

PATHOPHYSIOLOGY

Diseases such as gastroenteritis, diabetic ketoacidosis or Addison's disease cause their own specific changes in fluid and electrolyte balance, but there are non-specific changes which occur in response to any form of injury or inflammation, which have important clinical implications, particularly for surgical patients.

Response to injury

In the 1930s, Cuthbertson[12,13] described the metabolic changes, which occur in response to injury (including surgery and sepsis), as an increase in metabolic rate and protein breakdown to meet the requirements for healing. These changes were later shown to be due to neuroendocrine and cytokine changes and to occur in three phases (**Fig. 1.6**).

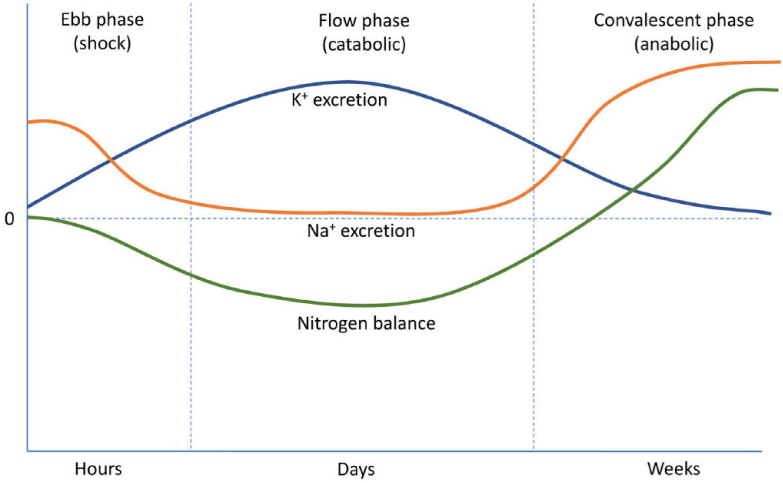

Fig. 1.6: The phases of the metabolic response to injury.

The ebb or shock phase is brief and is modified by resuscitation. This gives way to the flow or catabolic phase, the length and intensity of which depends on the severity of injury and its complications. As inflammation subsides, the convalescent anabolic phase of rehabilitation begins. In parallel with these metabolic changes there are changes in water and electrolyte physiology[14-16]. During the flow phase, there is an increase in ADH and aldosterone secretion leading to retention of salt and water with loss of potassium. These changes are exacerbated by any reduction in blood or ECF volume.

The normal, if somewhat sluggish, ability to excrete a salt and water load is further diminished, leading to the risk of ECF expansion and oedema if excessive salt and water are administered[14,17,18]. The response to injury also implies that oliguria is a normal response to surgery, and does not necessarily indicate the need to increase the administration of salt and water or plasma expanders unless there are also indications of intravascular volume deficit, e.g. from postoperative bleeding[19]. Salt and water retention after injury can be seen teleologically as a mechanism to protect the ECF and circulating volume. It also explains why sick patients can be overloaded easily by excessive salt and water administration during the flow phase. Since water as well as salt is retained, it is also easy to cause hyponatraemia by giving excess water or hypotonic fluid. Even after uncomplicated elective surgery, the capacity of the kidney

to dilute the urine is impaired for several days[3]. It is important, therefore, to administer crystalloids, not only in the correct volume but also with the appropriate electrolyte concentration. In the presence of the response to injury, the kidneys are unable to correct fully for errors in prescribing. This is further impaired in patients with acute kidney injury (AKI).

The convalescent phase of injury is characterised not only by the return of anabolism but also by a returning capacity to excrete any excess salt and water load that has been accumulated. These periods have been termed the 'sodium retention phase' and the 'sodium diuresis phase' of injury[18].

Potassium (K^+)

Potassium losses after surgery, sepsis and trauma are due not only to increased excretion in response to neuroendocrine mechanisms (e.g. the RAAS), but also to protein and glycogen catabolism. As intracellular protein is broken down and its constituent amino acids are released from cells, intracellular negative charges are lost and K^+, with its balancing positive charges, passes into the ECF to be excreted. In situations where catabolism is extreme and renal function is impaired, the outflow of potassium from the cells may exceed the capacity of the kidney to excrete it, causing dangerous hyperkalaemia. Conversely, in the convalescent phase, as net intracellular protein and glycogen anabolism are restored, the cells take up potassium again and the patient's potassium intake has to be increased to prevent hypokalaemia.

Transcapillary escape rate of albumin

The response to injury, inflammation and sepsis also results in an increase in the size of the pores in the capillary membrane and the transcapillary escape rate of albumin increases from about 5%/h in health to 13-15%/h[7]. These figures represent an average of all tissues in the body. There is, however, considerable variation from one organ to another, being higher in the liver than the skin, for example. This increase in albumin escape in response to inflammation can last from a few hours to several days, depending on the severity and duration of the underlying stimulus. Albumin leaks from the intravascular compartment into the interstitial space in association with water and sodium. This results in a net contraction of the intravascular compartment and expansion of the interstitial space (**Fig. 1.7**). As the return of albumin to the circulation via the lymphatics is unchanged, the net result is an intravascular hypovolaemia with interstitial oedema.

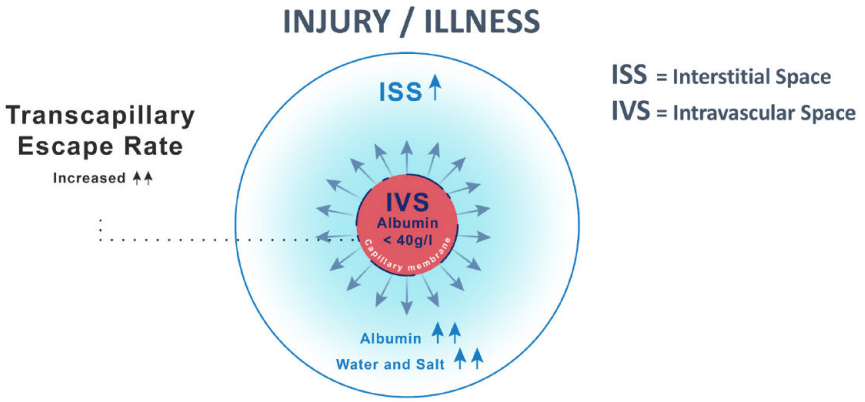

Fig. 1.7: Effects of an increase in the transcapillary escape rate of albumin.

Endothelial glycocalyx

The endothelial glycocalyx is a web of membrane-bound glycoproteins and proteoglycans on the luminal side of endothelial cells in the microcirculation, helping to maintain the function and integrity of the capillary-interstitial space interface. This interface can be damaged during the response to injury and inflammation and also by increased hydrostatic pressure caused by excessive intravenous fluid administration[20] (**Fig. 1.8**). Dysfunction of the endothelial glycocalyx in different organs secondary to inflammation or fluid resuscitation increases membrane permeability and the tendency to develop interstitial oedema.

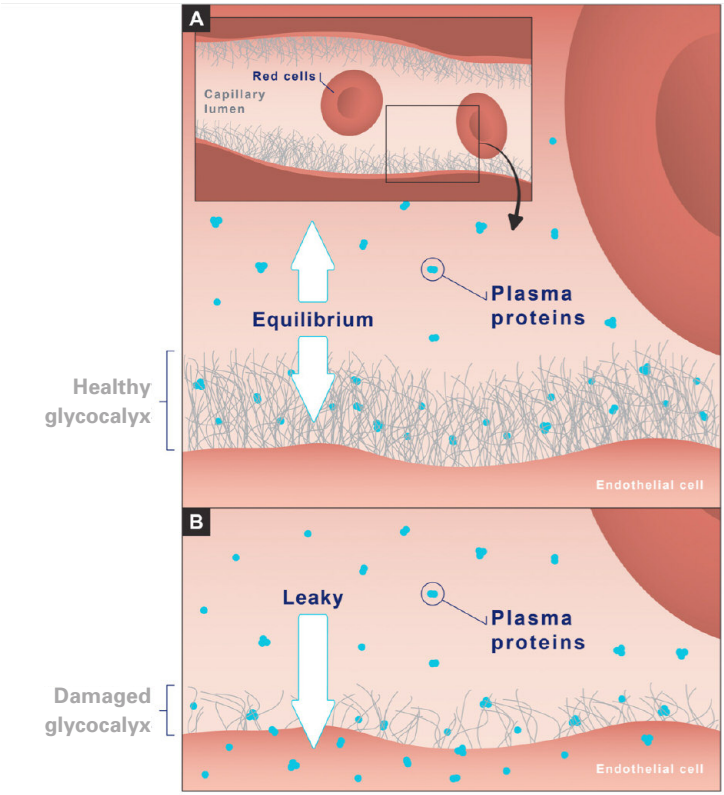

Fig 1.8: The endothelial glycocalyx in health and disease (Modified and redrawn from Myburg and Mythen[20]).

CONCLUSION

Appropriate fluid therapy depends on an understanding of the underlying physiology and pathophysiology and also of external and internal fluid balance in health and disease.

Chapter 2: AGEING AND FLUID BALANCE

INTRODUCTION

In the Western world the proportion of the population aged over 65 years is increasing steadily and in the UK is set to double by the year 2050[21]. This group also forms a high proportion of patients requiring surgery or presenting to hospital with fluid and electrolyte problems[22-24]. Ageing is associated with diminished reserve capacity of many organs, including the kidneys[25], causing increased susceptibility to both and water and electrolyte deficit and overload. Deficit of as little as 2% of total body water can cause significant impairment in physical, visual, psychomotor and cognitive performances[26]. One study reported a 17% 30-day mortality in this group admitted to hospital with dehydration, and a 1-year mortality of 50%[27].

The hospital population increasingly reflects this demographic change. In contrast to younger patients, the elderly often have multiple comorbidities requiring more complex management and have decreased functional reserve of organs, e.g. heart, lungs and kidney. They also suffer from the consequences of polypharmacy. It is, therefore, particularly necessary to have an integrated approach to this vulnerable group of patients and to assess the combined effect of these factors (**Tables 2.1** and **2.2**).

Table 2.1: Some risk factors for salt and water depletion in the older adult.

- Limited access to fluids from physical and mental disability
- Cognitive impairment
- Deliberate limitation of intake due to incontinence
- Polypharmacy (e.g. diuretics, sedatives, antidepressants, etc.)
- Lower socioeconomic background
- Living alone and social deprivation
- Pre-existing comorbidities
- Gastrointestinal disease (e.g. diarrhoea, vomiting, stomas)
- Impaired renal function
- Impaired thirst sensation
- Hot weather

Table 2.2: Some risk factors for salt and water overload in the older adult.

- Congestive heart failure
- Impaired renal function
- Liver disease
- Malnutrition
- Iatrogenic (e.g. surgery, intravenous fluid therapy)
- Obesity

PATHOPHYSIOLOGICAL BACKGROUND

With reductions of up to 50% in lean body mass in old age, total body water is reduced by 10-15% with an increased ECF:ICF ratio[22]. This and the renal structural and functional changes, associated with ageing, increase the risk that crystalloid administration can cause excessive ECF expansion, leading to peripheral and even pulmonary oedema. Older patients are also at risk of developing hyponatraemia from the administration of excessive volumes of hypotonic fluids. Renal changes, with the impaired ability to retain salt and water, also increase the risk of salt and water depletion, which is exacerbated by diuretics and by hot weather. In 2003, in France, a heat wave caused a 200% increase in mortality associated with fluid and electrolyte deficits in the older population[28].

Ageing is also associated with reduced serum concentrations of renin and aldosterone and a diminished renal tubular response to aldosterone. Atrial natriuretic peptide concentrations may be increased. These factors lead to a decreased capacity to maintain salt and water balance in the face of increased losses, or of diminished or excessive intake.

A blunted thirst response combined with reduced concentrating ability of the kidney increases the risk of developing a hyperosmolar state[29-31]. This risk is even greater in those with dementia since they often forget to drink.

Both hyper- and hyponatraemia, determined by the relative balance between salt and water, are significant problems in older adults, with hyponatraemia being more common. In a hospital population, a seven-fold increase in mortality has been reported in those with hypernatraemia compared with age-matched controls[32]. Among those undergoing surgery, mortality in those with hypernatraemia was 12.7% compared with 2.3% in those with normal serum sodium concentrations[33]. A prospective study of 200 older adults admitted to hospital in the UK showed that 37% were dehydrated on admission (serum osmolality >300 mOsm/kg) and were six times more likely to die in hospital than those with normal hydration[24]. Hyponatraemia is an independent risk factor for bone fractures and for increased mortality in those admitted for orthopaedic surgery[34,35].

Impaired renal function also makes older adults more vulnerable to hyperkalaemia, with the risk being higher in those taking angiotensin converting enzyme (ACE) inhibitors. On the other hand, hypokalaemia is not uncommon, particularly among those on diuretic therapy.

DIURETICS AND OTHER DRUGS

Diuretics and other medications either singly or in combination have significant effects on salt and water balance. If used inappropriately, these drugs may precipitate a number of complications, many of which require hospital admission[22].

Effects on salt and water balance

A high proportion of preventable hospital admissions among older adults are due to salt and water depletion caused by diuretics, the effects of which are often monitored inadequately. Patients should be educated in the management of these drugs and taught to stop them in the face of intercurrent illnesses[36], which reduce intake or increase losses of salt and water. Inappropriate continuation frequently precipitates fluid and electrolyte deficits. Patients receiving loop diuretics for heart failure may also be taught to monitor their fluid balance by daily weighing, taking the minimum dose required to maintain

zero balance. This approach should be tailored to the individual patient's circumstances and clinical features. Also, the high sodium content of many commonly prescribed drugs (e.g. antibiotics) can result in salt overload and should be taken into account when assessing fluid and electrolyte balance.

Effects on potassium balance

Medications such as ACE inhibitors, potassium sparing diuretics (e.g. spironolactone) and non-steroidal anti-inflammatory drugs interfere with potassium homeostasis and may result in hyperkalaemia.

SURGERY

Older adults undergoing surgery or being treated for acute trauma are at even greater risk than younger patients of developing salt and water depletion or excess. If possible, any such abnormalities should be corrected before surgery is undertaken since they impose an increased risk of morbidity and mortality[33]. Perioperative management of such patients is described in **Chapter 16**.

CONCLUSION

When treating patients in the older age group one should have a high index of suspicion that a fluid and electrolyte abnormality may already exist, make a careful search for its cause and treat it appropriately. It is important to be aware of the diminished capacity of such patients to maintain fluid and electrolyte homeostasis in the face of challenges and to devise a management plan which takes account of this and seeks to prevent problems rather than having to treat them when they have already occurred.

Chapter 3: DEFINITIONS

Much confusion in the diagnosis and treatment of fluid and electrolyte disorders is caused by loose and ambiguous terminology. The term 'dehydration', for example, meaning lack of water, is often used carelessly and imprecisely to include salt and water lack or, even more confusingly, intravascular fluid depletion. We, therefore, make a plea for the use of precise diagnostic terms, which indicate clearly the nature of the deficit or excess and the treatment required (e.g. salt and water depletion, plasma volume deficit, etc.).

Anabolism – the synthesis of large molecules from small ones, e.g. protein from amino acids or glycogen from glucose.

Catabolism – the breakdown of large molecules into small ones, e.g. protein to amino acids or glycogen to glucose.

Total body water (TBW) – percentage of body composition consisting of water, approximately 60% of body weight, less in obesity and more in infants. It is the sum of the intracellular and extracellular water in the body.

Intracellular fluid (ICF) volume – that part of the TBW contained within the cells, approximately 40% of body weight and 2/3^{rds} of TBW. Muscle cells contain 75% water and fat cells have <5% water.

Extracellular fluid (ECF) volume – that portion of the TBW outside the cells, approximately 20% of body weight and 1/3rd of TBW, sustained osmotically mainly by sodium and its associated anions (e.g. Cl^- and HCO_3^-).

Interstitial fluid volume – that portion of the ECF outside the circulation and surrounding the cells.

Intravascular fluid volume

- the **total blood volume** consisting of red and white cells and plasma. May be estimated at approximately 6-7% of the body weight.
- the **plasma volume** is that part of the ECF contained within the circulation and supported oncotically by the plasma proteins, separated from the interstitial fluid by the capillary membrane. Comprises approximately 3-4% of the body weight.
- the **effective circulatory volume** refers to that part of the intravascular fluid volume that is in the arterial system at any one time (normally 700 ml in a 70 kg man) and is effectively perfusing the tissues.

Salt – in chemistry this is used to describe a whole family of compounds such as $MgSO_4$, $FeSO_4$, $CaCl_2$, etc. but colloquially and in clinical practice it has come to mean NaCl, and that usage will be followed in this book.

Electrolyte – a substance whose components dissociate in aqueous solution into positively (cation) and negatively (anion) charged ions. For example, sodium chloride in solution (saline), dissociates into Na+ and Cl^-. Other electrolytes of physiological importance include Ca^{2+}, Mg^{2+}, K^+, PO_4^{2-}, etc. Glucose is not an electrolyte as it does not dissociate in solution. In health the total number of positive charges balances the number of negative charges to achieve electrical neutrality.

Dehydration – the term 'dehydration' strictly means lack of water (hypertonic dehydration), yet it is also used colloquially to mean lack of salt and water (e.g. isotonic dehydration) or even more loosely to describe intravascular volume depletion. The terms 'wet' and 'dry' are applied to patients with similarly imprecise meaning. We make a plea for confining the use of dehydration to mean 'water lack' and for using unambiguous terms such as 'salt and water depletion', 'blood loss', 'plasma deficit', and so forth, since these are clear diagnoses indicating logical treatments. It may, however, be used legitimately to describe fluid deficit from sweating, remembering that a litre of sweat contains up to 50 mmol Na^+ This may require salt as well as water replacement in tropical conditions. Severe dehydration can result in acute kidney injury.

Salt and water depletion – this is one of the commonest problems in hospital practice, arising from such conditions as diarrhoea and vomiting, ketotic and non-ketotic diabetic decompensation, and diuretic excess. The relative proportion of salt or water lack depends on the source of the loss and the amount of water, which the patient has consumed in order to assuage thirst: it is reflected in the serum concentrations of sodium and chloride.

Intravascular volume depletion – this signifies a deficit in plasma or total blood volume, as in burns or haemorrhage, or a reduction in circulating volume secondary to a reduction in total ECF due to salt and water loss. The terms 'plasma volume depletion' or 'blood volume deficit' are even more specific.

Salt and water excess – this is most commonly iatrogenic, resulting from excessive administration of saline, but is, of course, a feature of congestive heart failure and other oedema producing conditions. It takes 2-3 litres of salt and water excess before the extracellular fluid is expanded sufficiently for oedema to become clinically apparent. Again, the relative proportions of salt and of water overload, but not the absolute amount of either, are reflected in the serum sodium and chloride concentrations.

Solution – fluid consisting of a solvent, e.g. water, in which a soluble substance or solute, e.g. sugar or salt, is dissolved.

Crystalloid – a term used commonly to describe all clear glucose and/or salt containing fluids for intravenous use (e.g. 0.9% saline, Hartmann's solution, 5% dextrose, etc.).

Colloid – a fluid consisting of microscopic particles (e.g. starch, gelatin or protein) suspended in a crystalloid and used for intravascular volume expansion (e.g. 6% hydroxyethyl starch, 4% succinylated gelatin, 20% albumin, etc.).

Balanced crystalloid – a crystalloid containing electrolytes in a concentration as close to plasma as possible (e.g. Ringer's lactate, Hartmann's solution, Plasmalyte 148, Sterofundin ISO, etc.). They should affect acid-base equilibrium minimally, when compared with 0.9% saline. Recently, the term "balanced" crystalloid has been used to indicate intravenous fluids with low chloride (near physiological) content, as they do not produce the hyperchloraemic acidosis associated with 0.9% saline.

Buffer – a solution which resists changes in pH when acid or alkali is added to it. A buffer solution is an aqueous solution of a mixture of a weak acid and its conjugate base, or vice versa. Its pH changes very little when a small amount of strong acid or base is added to it. Buffer systems in the blood are used as a means of keeping pH at a nearly constant value in a wide variety of chemical applications. In nature, there are many systems that use buffering for pH regulation. For example, the bicarbonate buffering system is used to regulate the pH of blood.

Osmosis – this describes the process by which water moves across a semi-permeable membrane (permeable to water but not to the solutes) from a weaker to a stronger solution until the concentration of solutes are equal on the two sides.

This force is termed osmotic pressure or, in the case of colloids e.g. albumin, oncotic pressure. It is proportional to the number of atoms/ions/molecules in solution and is expressed as mOsm/l (**osmolarity**) or mOsm/kg of solution (**osmolality**). E.g. the osmolarity of 0.9% saline is 308 mOsm/l, but the osmolality is 305 mOsm/kg (308 mOsm in 1.009 kg).

In clinical chemistry the term 'osmolality' is the one most often used. For example, out of approximately 280-290 mOsm/kg in extracellular fluid the largest single contributor is sodium chloride. This dissociates in solution and, therefore, its component parts Na^+ and Cl^- exert osmotic pressure independently i.e. Na^+ (140 mmol/kg), contributes 140 mOsm/kg, and Cl^- (100 mmol/kg) contributes 100 mOsm/kg. Additional balancing negative charges come from bicarbonate (HCO_3^-) and other anions. In the intracellular space K^+ is the predominant cation (see below).

Because glucose does not dissociate in solution, each molecule, although much larger than salt, behaves as a single entity in solution and at a concentration of 5 mmol/L, contributes only 5 mOsm/kg to the total osmolality of plasma.

The cell membrane and the capillary membrane are both partially permeable membranes although not strictly semi permeable in the chemical sense (see below). They act, however, as partial barriers dividing the extracellular (ECF) from the intracellular fluid (ICF) space, and the intravascular from the interstitial space. Osmotic or oncotic shifts occur across these membranes, modified by physiological as well as pathological mechanisms.

Tonicity – the osmotic pressure or tension of a solution, usually relative to that of blood. Unlike osmotic pressure, tonicity is influenced only by solutes that cannot cross the membrane, as only these exert an effective osmotic pressure. Solutes able to cross the membrane freely do not affect tonicity because they will always be in equal concentrations on both sides of the membrane. Infusion solutions are, therefore, described as hypotonic, isotonic or hypertonic. E.g. 5% dextrose is isotonic at the point of infusion (in order to prevent haemolysis), but once its glucose content has been metabolised, it becomes hypotonic, giving a net gain of free water.

Free water – solute-free water (e.g. 1 L of 5% dextrose provides 1 L of free water as the dextrose is metabolised, whereas 1 L of 0.9% saline provides no free water).

Free water clearance is defined as the volume of plasma that is cleared of solute-free water per unit time. It is, therefore, greater in response to hypotonic fluid administration than in states of dehydration.

Anion gap – the difference between the plasma concentration of the major cation Na^+ and the major anions Cl^- and HCO_3^-, giving a normal anion gap of 5-11 mmol/L. It is increased in metabolic acidosis due to organic acids as in diabetic ketoacidosis, lactic acidosis, renal failure, and ingested drugs and toxins.

$$\text{Anion gap (mmol/L)} = [Na^+] - ([Cl^-] + [HCO_3^-])$$

The anion gap is normal in hyperchloraemic acidosis (e.g. after excess 0.9% saline administration). It is, therefore, useful in the differential diagnosis of metabolic acidosis, although specific measurement of organic acids such as β-hydroxy butyrate or lactate may also be necessary to define the problem.

Strong ion difference (SID) – Stewart[37] has described a mathematical approach to acid-base balance in which the strong ion difference (SID (mmol/L)=$[Na^+]+[K^+]-[Cl^-]$) in the body is the major determinant of the H^+ ion concentration. A decrease in the strong ion difference is associated with a metabolic acidosis, and an increase with a metabolic alkalosis. A change in the chloride concentration is the major anionic contributor to the change in H^+ homoeostasis. Hyperchloraemia caused by a saline infusion, therefore, will decrease the strong ion difference and result in a metabolic acidosis.

e.g. If Na^+ is 140 mmol/L, K^+ is 4 mmol/L and Cl^- is 100 mmol/L, the SID is 44 mmol/L. The normal range is 38-46 mmol/L.

Base excess – Base excess is defined as the amount of strong acid that must be added to each litre of fully oxygenated blood to return the pH to 7.40 at a temperature of 37°C and a P_aCO_2 of 40 mmHg (5.3 kPa). A base deficit (i.e., a negative base excess) can be correspondingly defined in terms of the amount of strong base that must be added.

Acidaemia and Alkalaemia – An increase in the H^+ ion concentration or a decrease in the pH is called acidaemia; a decrease in the H^+ ion concentration or an increase in the pH is called alkalaemia.

Acidosis and Alkalosis – Processes that tend to raise or lower the H^+ ion concentration are called acidosis and alkalosis respectively. These may be respiratory, metabolic or a combination of both. CO_2 retention causing a rise in P_aCO_2 in respiratory failure leads to respiratory acidosis, and hyperventilation with a consequent lowering of P_aCO_2 leads to respiratory alkalosis. Accumulation of organic acids such as lactate or β-hydroxybutyrate or of mineral acidic ions such as chloride cause a metabolic acidosis in which arterial pH falls below 7.4, HCO_3^- is reduced and P_aCO_2 falls as the lungs attempt to compensate by blowing off more CO_2. This is called a compensated metabolic acidosis. Similarly, ingestion of alkalis such as HCO_3^- or loss of gastric acid cause a rise in pH and a metabolic alkalosis.

External balance – is the difference between intake of fluid and electrolytes from food and drink (or enteral or parenteral fluid therapy) and loss via the kidneys, gastrointestinal tract, skin and lungs.

Internal balance – is the redistribution of fluid and electrolytes between different body compartments (e.g. between the intravascular and interstitial space or between ECF and ICF). It also includes shifts into spaces such as the pleural and peritoneal cavities or into the gastrointestinal tract due to pooling of secretions as in postoperative ileus or intestinal obstruction.

Insensible loss – loss from the skin by sweat or evaporation, from the lungs as water vapour or from wounds by exudation or evaporation. Under normal clinical conditions it is difficult to quantify such losses, except by changes in weight. One of the major limitations of fluid balance charts is that this loss of fluid can only be estimated and not quantified. This could range from 500-1000 ml/day, or even higher, depending on ambient temperature, body temperature, respiratory rate, burn surface area, etc.

Estimated glomerular filtration rate (eGFR) – is a mathematically derived value based on a patient's serum creatinine concentration, age and sex. This is usually calculated by the laboratory analysing the blood sample and reported along with the serum creatinine result. "Normal" GFR is usually >90 ml/min/1.73 m^2. (Note the correction for body surface area "per 1.73 m^2" which is important for certain patient groups, e.g. amputees, extremes of body habitus.)

Acute kidney injury (AKI) – a rapid reduction in kidney function occurring over hours or days, resulting in a rise in blood urea and creatinine and disturbance of fluid and electrolyte balance[38]. New definitions and staging systems for AKI are based on rises in serum creatinine or reductions in urine output (see **Chapter 10**).

Acute kidney disease (AKD) – the concept of AKD is relatively new and refers to the scenario where there is a decrease in kidney function over a period of less than three months, and the change in creatinine value does fit the definition of AKI. The following criteria have been proposed; a reduction in eGFR by >35% or an increase in creatinine by >50% in <3 months[39].

Chronic kidney disease (CKD) – a slow and prolonged reduction in kidney function that is sustained for more than 3 months[39]. There is an established definition and staging system for CKD based upon the level of eGFR and albuminuria (see **Chapter 11**).

Sepsis – defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality[40].

Chapter 4: ACID-BASE BALANCE

INTRODUCTION

Maintenance within narrow limits of the normal acid base composition of the '*milieu interieur*' is essential for the optimal function of tissues[10,41-43]. The kidneys together with the lungs and liver play an essential role in the maintenance of normal acid-base balance and arterial blood pH (**Table 4.1**). The kidneys remove acid and regenerate bicarbonate, the lungs can regulate the removal of acid (CO_2) by varying respiratory rate and the liver removes and recycles lactate. Therefore, patients with advanced CKD stage 4-5 (eGFR <30 ml/min/1.73 m^2), liver disease or underlying respiratory disease are at increased risk of developing acid-base abnormalities at times of acute illness.

Table 4.1: Normal arterial blood acid-base measurements.

pH	7.35-7.45
P_aO_2 (kPa)	10.7-16.0
P_aCO_2 (kPa)	4.7-6.0
HCO_3^- (mmol/L)	22-26
Base excess (mmol/L)	-2 - +2
Anion gap (mmol/L)	5 - 11

A normal blood pH of 7.35-7.45 is maintained by different buffering systems which include the blood, kidney, lung and liver buffering system described below.

The blood buffering system, which is dependent upon

- bicarbonate (HCO_3^-)
  - the relative proportion of carbonic acid from CO_2 and of HCO_3^- is defined by the Henderson-Hasselbach equation[44,45]. Note that the pH is determined by the ratio of HCO_3^- to CO_2.

$$pH = 6.10 + \log \frac{\left[HCO_3^-\right]}{0.03\,pCO_2}$$

- haemoglobin
- phosphate (organic and inorganic)
- bone and its calcium salts

The kidney buffering system which

- controls hydrogen H^+ and HCO_3^- excretion or reabsorption as well as the conversion of ammonia (NH_3) to ammonium (NH_4^+) in the urine.

The lung buffering system, which controls

- CO_2 in the blood, increasing expired CO_2 when more is produced or to compensate for metabolic acidosis.

The liver buffering system which

- removes and recycles the large amounts of lactate produced by anaerobic respiration (Cori cycle).

Disease states can disrupt this finely balanced system resulting in a dangerously low (pH <7.1) or dangerously high pH (pH >7.6). Specific patient management will depend upon the clinical status of the patient and the underlying cause of the acid-base disorder. This chapter will provide a simple description of the most common forms of the simple acid-base disorders. Expert advice should be sought if it is suspected that the patient has a more complex form of acid-base disorder.

APPROACHES TO ACID-BASE BALANCE

There are essentially two different ways to approach acid-base disorders.

- The traditional Schwartz-Bartter approach, which accepts the Bronsted-Lowry definition of acids as proton donors and bases as proton acceptors. The hydrogen ion concentration is a function of the ratio between the carbon dioxide (CO_2) and the serum bicarbonate (HCO_3^-). This traditional approach utilises the anion gap calculation to classify acid-base disturbances and is the method used in this chapter.
- The Stewart approach[37,46], termed the Strong Ion Difference (SID), is based on the principle that the serum bicarbonate concentration does not alter blood pH. This approach is favoured by intensivists and anaesthetists and is described separately towards the end of this chapter.

CLINICAL PRESENTATION

It is important in every acutely ill patient to consider whether there may be an underlying acid-base disturbance. Serum bicarbonate and chloride are not standard components of all urea and electrolyte (U&E) reports and may have to be specifically requested. Severe acidaemia (pH <7.1) results in impaired cardiac function and vascular tone. Severe alkalaemia (pH >7.6) results in irritability of cardiac and skeletal muscle.

Conditions commonly causing acid-base disorders include:

- vomiting/diarrhoea
- shock
  - cardiogenic
  - septic
  - hypovolaemic
- acute kidney injury

- respiratory failure
- altered neurological status
  - coma
  - seizures
- decompensated diabetes mellitus
- hypokalaemia or hyperkalaemia
  - potassium metabolism is intimately linked to acid-base balance
- prolonged and excessive infusions of 0.9% saline causing hyperchloraemic metabolic acidosis (as 0.9% saline has a chloride concentration that is 1.5 times that of plasma)

If an acid-base disturbance is suspected from clinical features, the following blood tests should be performed initially:

- Urea, creatinine and electrolytes (U&Es)
- Bicarbonate
- Chloride
- Glucose
- Arterial blood gases (including lactate)

These investigations can then be used in a step-by-step approach to identify the type of acid-base disorder

- assess the pH to determine whether acidaemia or alkalaemia
- a change in HCO_3^- and base excess (BE) indicates a metabolic process
- a change in P_aCO_2 indicates a respiratory process
- determine whether
  - simple disorder, i.e. either metabolic or respiratory process alone
  - mixed disorder, i.e. a combination of a metabolic and respiratory process. There will be evidence of compensatory changes in either HCO_3^- or P_aCO_2
- calculate the anion gap
  - determined primarily by negative charge on serum proteins, particularly albumin
  - normal anion gap = 5-11 mmol/L

$$\text{Anion Gap} = [Na^+] - ([HCO_3^-] + [Cl^-])$$

  - in the clinical setting of hypoalbuminaemia the normal anion gap is adjusted downward by 2.5 mmol/L for every 10 g/L reduction in serum albumin concentration
  - an increase in anion gap indicates a tendency towards acidosis and a decrease a tendency towards alkalosis.

Simple acid-base disorders

Table 4.2 demonstrates simple acid-base disorders in terms of the primary change in bicarbonate or carbon dioxide, the compensatory changes that occur and the effect on pH. By a simple rule of thumb, in simple acid-base disorders the acid-base buffer pair change in the same direction. If they change in the opposite direction the disorder must be mixed.

Table 4.2: Simple acid-base disorders.

	Primary change	Primary change in pH	Physiological compensation
Metabolic acidosis	↓ HCO_3^-	↓ pH	↓ P_aCO_2
Metabolic alkalosis	↑ HCO_3^-	↑ pH	↑ P_aCO_2
Respiratory acidosis	↑ P_aCO_2	↓ pH	↑ HCO_3^-
Respiratory alkalosis	↓ P_aCO_2	↑ pH	↓ HCO_3^-

Causes of simple acid-base disorders

The cause of an acid-base disorder is often apparent from the clinical presentation. Metabolic acidosis is best considered as associated with a high anion gap (**Table 4.3**) or a normal anion gap (**Table 4.4**).

Table 4.3: Causes of a 'high anion gap' metabolic acidosis.

Ketoacidosis
• diabetes mellitus
Lactic acidosis
• tissue hypoxia
• liver failure
• metformin
Drug toxicity
• ethylene glycol
• methanol
• salicylate (aspirin)
Kidney disease
• chronic kidney disease
• acute kidney injury

Table 4.4: Causes of a 'normal anion gap' (hyperchloraemic) metabolic acidosis.

Gastrointestinal HCO_3^- loss
• diarrhoea
• fistulae
Renal HCO_3^- loss
• renal tubular acidosis
• acetazolamide
Excessive infusion of 0.9% saline

'High anion gap' metabolic acidosis – can be caused by four broad categories of disorders including ketoacidosis, lactic acidosis, poisonings, AKI or CKD.

- Ketosis occurs when there is a lack of insulin or hypoglycaemia. To compensate, fatty acids are oxidised to produce energy resulting in the production of ketoacids as a by-product.
  - Severe ketoacidosis occurs secondary to insulin deficiency (see **Chapter 14**)
  - Moderate ketosis may also occur with prolonged starvation or in alcoholics
- Lactic acidosis is subdivided into
  - Type A lactic acidosis - secondary to insufficient oxygen delivery to the tissues
    - hypovolaemic shock
    - cardiogenic shock
    - septic shock
  - Type B lactic acidosis – impaired gluconeogenesis causing inability to clear lactate
    - liver failure
    - metformin
- Drug toxicity can be subdivided into
  - ethylene glycol/methanol
    - metabolism generates glycolate from ethylene glycol and formate from methanol
    - associated with an elevated osmolal gap
    - measured serum osmolality - calculated osmolality
    - calculated osmolality = $2 \times [Na^+]$ + glucose + urea
    - intoxication likely if measured serum osmolality - calculated osmolality >25 mOsm/kg
    - clinically presence of calcium oxalate crystals in the urine suggests ethylene glycol toxicity
  - salicylates
    - may result in a metabolic acidosis, respiratory alkalosis or a mixed acid-base disorder
- Kidney disease
  - chronic kidney disease and acute kidney injury result in reduced
    - excretion of the daily acid load (sulphates, phosphates and organic anions)
    - regeneration of bicarbonate

'Normal anion gap' (hyperchloraemic) metabolic acidosis – can be caused by excess saline infusion, or by gastrointestinal or renal bicarbonate loss. Rarer causes include inorganic acid intake.

- Gastrointestinal bicarbonate loss results from
  - diarrhoea and external fistulae from the pancreas and small bowel
  - increased chloride absorption occurring as a compensatory mechanism and resulting in a hyperchloraemic metabolic acidosis with a normal anion gap
- Renal bicarbonate loss results from
  - renal tubular acidosis (RTA), conditions that are caused either by failure to reabsorb bicarbonate from the proximal tubule (type II RTA) or bicarbonate wasting from the distal tubule (type I RTA)
  - acetazolamide (carbonic anhydrase inhibitor) which inhibits bicarbonate reabsorption

Metabolic alkalosis – can occur in association with fluid depletion or mineralocorticoid excess (**Table 4.5**). In metabolic alkalosis associated with fluid depletion there is loss of fluid rich in H^+ or Cl^- from the stomach, kidneys or skin. In the absence of fluid depletion, a metabolic alkalosis may occur in hyperaldosteronism, due to enhanced renal H^+ secretion.

Table 4.5: Causes of metabolic alkalosis.

Fluid depletion
• vomiting
• gastric suction
• diuretics
Hyperaldosteronism
Cushing's syndrome
Alkali (e.g. bicarbonate) ingestion
• antacids

Respiratory acidosis – may occur acutely due to respiratory depression secondary to drugs or neurological damage, respiratory muscle weakness, chest injury or acute airway obstruction. In some cases of chronic obstructive airway disease P_aCO_2 may also be permanently elevated, usually partially compensated by an increase in plasma HCO_3^-.

Existing respiratory disease may be exacerbated perioperatively by atelectasis, respiratory infection, retained sputum, abdominal distension, splinting of the diaphragm, pain from the wound or high doses of opiates. Epidural analgesia may be advantageous in such conditions. In severe cases, particularly those with prior lung disease, bronchial suction and mechanical ventilation may be necessary. Early mobilisation and chest physiotherapy is also vital in many cases.

Respiratory alkalosis – is due to hyperventilation, causing a low P_aCO_2 and in chronic cases, some compensatory reduction in HCO_3^-. It may be iatrogenic due to deliberate or mistakenly overenthusiastic artificial ventilation, or secondary to hyperventilation from anxiety or distress. It sometimes causes paraesthesiae, tetany and chest pain.

MANAGEMENT

The principles of management involve correcting any abnormalities of fluid and electrolyte balance (e.g. hypovolaemia, salt and water deficit). The underlying cause for the acid-base disorder (e.g. ketoacidosis, AKI, sepsis) must be diagnosed and managed promptly. In general, specific therapy (e.g. bicarbonate administration for acidosis) to correct the $[HCO_3^-]$ or P_aCO_2 is only contemplated if the acid-base disorder is affecting organ function or if the pH is <7.1 or >7.6.

Patients identified as having an AKI and metabolic acidosis secondary to ethylene glycol or methanol intoxication need immediate referral to the renal team for consideration of intermittent haemodialysis to remove the toxin. Fomepizole, an alcohol dehydrogenase inhibitor is the preferred first line therapy to prevent the metabolism of ethylene glycol or methanol to their respective toxic metabolites. Additional

management should be guided by advice from a poisons centre, but may include the intravenous infusion of alcohol (ethanol) to prevent the breakdown of ethylene glycol and methanol to their toxic metabolites by alcohol dehydrogenase if fomepizole is not available.

Mixed acid-base disorders

These are defined as the presence of more than one cause (e.g. metabolic and respiratory). The patient's history or a lesser or greater than predicted compensatory respiratory or renal response may raise suspicions of mixed acid-base disorder.

A normal pH in the setting of substantial changes in both serum HCO_3^- or arterial P_aCO_2 indicates a mixed-acid base disorder is present.

Stewart approach to acid-base disorders

The Stewart approach[37], termed the Strong Ion Difference (SID), is based upon the central tenet that serum bicarbonate does not alter blood pH. Stewart defined acids as ions that shift the dissociation equilibrium of water to a higher concentration of H^+ and a lower concentration of OH^-.

The SID is the difference between the completely dissociated cations and anions in the plasma. It is defined as the difference between the sum of the strong cations, Na^+, K^+, Ca^{2+} and Mg^{2+} and the sum of the net charge of the major strong cations, Cl^- and lactate.

$$SID = [Na^+ + K^+ + Ca^{2+} + Mg^{2+}] – [Cl^- + lactate] = 38\text{-}46 \text{ mmol/L}$$

An increase in the SID is associated with an increase in blood pH, an alkalosis, e.g. vomiting leads to a loss of chloride and a decrease in serum chloride levels resulting in an increase in SID and alkalosis. The Stewart approach, therefore, explains the alkalosis associated with vomiting as excessive loss of chloride.

A decrease in SID is associated with a decrease in blood pH, an acidosis, e.g. the excessive infusion of saline results in an increase in $[Cl^-]$ and, therefore, a decrease in SID and an acidosis. The Stewart approach, therefore, explains the hyperchloraemic metabolic acidosis associated with excessive saline infusion by the gain of chloride.

Conclusion

An acid-base disorder should be suspected in all seriously ill patients or those with an indicative history. It should be fully investigated to determine whether the changes have a metabolic or respiratory cause or a combination of the two. The aim of treatment should be to correct the underlying cause of the acid-base disorder, e.g. diabetic ketoacidosis. In severe cases it may be necessary in the short term to restore blood biochemistry towards normal, e.g. with bicarbonate infusions in acidosis.

Chapter 5: ASSESSMENT, MEASUREMENT AND MONITORING

INTRODUCTION

As in all clinical conditions, assessment of fluid and electrolyte status begins with a careful history and examination, followed by bedside and laboratory tests. The key features of assessment and monitoring of fluid balance are summarised in **Table 5.1**.

Table 5.1: Assessment and monitoring of fluid balance.

Parameter	Significance
History	Alerts to likelihood of fluid deficit (e.g. vomiting/diarrhoea/ haemorrhage) or excess (e.g. from intraoperative fluids). High fever may be associated with increased insensible loss.
Autonomic responses	Pallor and sweating, particularly when combined with tachycardia, hypotension and oliguria (shock) are suggestive of intravascular volume deficit, but can also be caused by other conditions, e.g. pulmonary embolus or myocardial infarction.
Capillary refill	Slow refill compatible with, but not diagnostic of volume deficit. It should be tested by pressure on the nail bed or pulp of the finger. If there is good blood flow, a pink colour should return in less than 2 seconds after pressure is removed. Can also be influenced by temperature, administration of inotropes or beta blockers, and by peripheral vascular disease.
Pulse rate	With intravascular fluid deficit pulse rate rises to maintain cardiac output, but this response may be masked by drugs (e.g. beta blockers, diltiazem) or electrolyte abnormalities (e.g. hyperkalaemia) which interfere with cardiac conduction.
Blood pressure	Cuff measurements may not always correlate with intra-arterial monitoring. Does not necessarily correlate with volume status or perfusion. Affected by drugs (important to review medication charts). Nonetheless, a fall is compatible with intravascular hypovolaemia, particularly when it correlates with other parameters such as pulse rate, urine output, etc. Systolic pressure does not usually fall until 30% of blood volume has been lost. Postural hypotension (fall in blood pressure between that measured in the recumbent and sitting or standing positions) may also indicate an intravascular or ECF volume deficit.
Jugular venous pressure (JVP)	Assessed by examination of the neck with the patient at 45° recumbency and observing the height of the filling level of the internal jugular vein above the clavicle.

Passive leg raising test	A bedside method to assess likely response to fluid administration. Best undertaken with the patient initially semi-recumbent and then tilting the entire bed through 45° or by lying the patient flat and passively raising their legs to greater than 45°. Signs of haemodynamic improvement (e.g. rise in blood pressure, decrease in tachycardia, improved peripheral perfusion) at 30–90 seconds suggest an intravascular volume deficit likely to respond to intravenous fluids. If the patient develops dyspnoea, it indicates that the patient may be fluid overloaded.
Skin turgor	Diminished in salt and water depletion, but decreased skin turgor can also be caused by ageing, cold and cachexia. Probably best assessed over the clavicles, but should not be relied upon to indicate salt and water depletion in the absence of supporting evidence.
Sunken facies	Most commonly due to starvation or wasting from disease, although compatible with salt and water depletion.
Dry mouth	A poor indicator. Compatible with salt and water depletion, but usually due to mouth breathing.
Oedema	The presence of pulmonary oedema should indicate the need to stop further intravenous fluid administration. Peripheral oedema (pedal and/or sacral) occurs in volume overload but can occur due to hypoalbuminaemia (check serum albumin concentration) or heart failure. It may also be due to interstitial fluid space expansion by salt and water, even in patients with a low intravascular fluid volume. Drug therapy (e.g. amlodipine) may cause local dependent oedema due to increased capillary permeability. Dependent oedema may also be caused by prolonged sedentary posture, particularly in the elderly.
Urine output	<30 ml/h (<0.5 ml/kg/h) is commonly used as an indication for fluid infusion, but in the absence of other features of intravascular hypovolaemia suggesting a pathological cause, it is usually due to the physiological oliguric response to surgery and requires no increase in fluid administration. It is more useful to average the urine output over 4 h in the postoperative patient who is not hypovolaemic. Urine quality (e.g. concentration, urine: plasma urea or osmolality ratio) is just as important, particularly in the complicated patient.
Weighing	24-h change in weight (performed under similar conditions) – best measure of change in water balance. Takes account of insensible loss. Simple to carry out by bedside. May be difficult in the critically ill.
Fluid balance charts	Inherently inaccurate in measurement and recording. They do not measure insensible loss. Large cumulative error may occur over several days. Good measure of changes in urine output, fistula loss, gastric aspirate, etc.

Serum biochemistry	Indicates ratio of electrolytes to water in the extracellular fluid. Serum sodium concentration is a poor indicator of whole body sodium status. Hyponatraemia most commonly caused by water excess. If change in water balance over 24 h is known, then change in serum sodium concentration can be a guide to sodium balance. Hypokalaemia, on the other hand, nearly always indicates the need for potassium supplementation. Blood bicarbonate and chloride concentrations measured on point of care blood gas machines are useful in patients with acid-base problems including iatrogenic hyperchloraemia from saline infusion. Blood urea reflects renal function and protein catabolism. Serum creatinine is used to measure renal function and is also influenced by muscle mass, being higher in muscular individuals than in those with muscle wasting.
Urinary biochemistry	Urinary sodium concentration may reflect renal perfusion and a low value (<20 mmol/L) is compatible with renal hypoperfusion (pre-renal AKI), although it is also a feature of the response to injury or to sodium depletion. Measurement of urinary potassium is helpful in assessing the cause of refractory hypokalaemia. Urinary urea excretion increases several-fold in catabolic states (e.g. sepsis) and is an indication for provision of additional free water to avoid hypernatraemia and uraemia. Urinary and serum creatinine are combined to measure creatinine clearance to assess renal function.
eGFR	The estimated glomerular filtration rate provides an estimation of renal function in the steady state, but not in AKI.

HISTORY

This gives the initial clue to the likely abnormality and the type and degree of deficit, e.g. a background of poorly controlled diabetes, a story of vomiting and/or diarrhoea, diuretics in an elderly patient who is confused, blood loss, burn injury, etc. All possible sources of fluid and electrolyte gain or loss should be explored.

DRUG HISTORY

It is also important, in the initial assessment of any patient, that careful attention be paid to drug prescription cards as a number of drugs may affect salt and water balance (e.g. diuretics, corticosteroids, laxatives, etc.) while others may contain significant amounts of sodium, potassium or chloride (e.g. some antibiotics which are sodium salts) (see **Chapter 6**). Also 0.9% saline is often used as a diluent or vehicle for administration of drugs and this may contribute to sodium and chloride overload. Each ml of 0.9% saline provides 0.15 mmol of sodium and chloride.

EXAMINATION

Physical signs of fluid deficit are indicative but not specific, and no conclusion should be drawn from any single feature (**Table 5.1**). The first indication of a falling intravascular volume is a decrease in central venous pressure (CVP), as evidenced by a fall in JVP. With progressive severity, pulse rate increases (**Fig. 5.1**), followed by a fall in blood pressure with pallor and sweating. The full-blown picture is called 'shock'. In contrast, pink warm peripheries, with rapid capillary refill after pressure and a negative passive leg raising test, are usually suggestive of an adequate circulation. Serial assessments of JVP, pulse, blood pressure and urine output are sufficient to monitor most patients, but in complex cases or in critical illness, bedside examination may need to be supported by invasive techniques for assessing cardiovascular function.

It should also be remembered that shock states due to volume depletion, cardiac causes, or sepsis share many similar features which require expert assessment to distinguish.

Dependent oedema is not necessarily due to salt and water overload but, particularly in the elderly, may be gravitational in origin due to prolonged sitting and immobility.

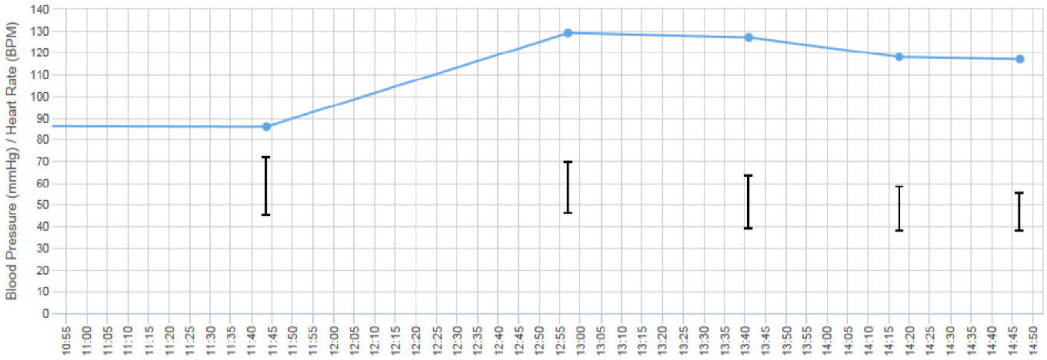

Fig. 5.1: Example of a vital signs chart showing a rising pulse rate and a falling blood pressure, indicating progressive intravascular hypovolaemia secondary to haemorrhage.

Examination of the jugular filling with the patient reclining at 45° should be routine. If the level is elevated above the clavicle, this may signify intravascular over-expansion by administered fluids, congestive heart failure, or both. If, however, no jugular filling is observed, then lower the patient slowly until filling is observed. If filling is still not seen or only seen with the patient nearly horizontal, then this may signify an intravascular volume deficit. This manoeuvre is valuable in assessing patients still receiving intravenous fluids some days after the acute phase of their illness has subsided and in whom recovery is slow or accompanied by complications. Such patients may have an expanded interstitial fluid space with oedema due to excess crystalloid administration, but a diminished blood or plasma volume due to continuing leak of blood, protein or serous fluid into wounds or inflamed areas. These findings may indicate the need for colloid (e.g. 20% salt-poor albumin) to expand the intravascular volume, improve renal blood flow and allow the excretion of the salt and water overload. If, on the other hand, the jugular venous pressure (JVP) is elevated, then immediate cessation of crystalloid administration, with or without diuretics, will correct the underlying imbalance.

MEASUREMENTS AND INVESTIGATIONS

Urine

As described above, the volume and concentration of urine are important indicators of renal function. Oliguria may be physiological postoperatively or indicative of intravascular or ECF deficit. If this is accompanied by a concentrated urine and a rising blood urea, it is termed pre-renal AKI, correctable by appropriate fluid replacement. A persisting low volume and concentration combined with a rising blood urea and creatinine suggest AKI due to intrinsic tubular damage has now developed, necessitating some form of renal replacement therapy (e.g. haemofiltration or haemodialysis). Changes in urine volume must, therefore, be interpreted in the light of accompanying features and circumstances.

In some acutely ill and postoperative patients urinary catheters may be required to monitor hourly urine output. However, they should not be used routinely because of the increased risks of urinary tract infection and catheter-related sepsis.

Nurses are often instructed to call junior doctors if the postoperative urine output falls below 30 ml/h. Consequently, the doctor often prescribes extra saline "just to be on the safe side". This commonly results in salt and water overload. In fact, such "oliguria" is usually a physiological response to surgery. While it is important to identify the patient who has become hypovolaemic and is in need of resuscitation, it is unlikely that a patient who appears well with warm pink peripheries and no tachycardia or tachypnoea needs volume expansion. Urine output in such patients should be averaged over four to six hours and interpreted in combination with serial trends in vital signs of circulatory adequacy. A recent study has shown that a perioperative urine output target of 0.2 ml/kg/h (i.e. 14 ml/h in a 70 kg patient) is not inferior to the standard target of 0.5 ml/kg/h (i.e. 35 ml/h in a 70 kg patient). This strategy reduces the volume of intravenous fluid administered without increasing the risk of developing AKI[47].

Fluid balance charts

Name: Date: 24 hour FLUID ALLOWANCE: YES ☐ _____ mls NO ☐

	INPUT (mls)						OUTPUT (mls)						
Time	Oral	IV	IV	Enteral	Other	TOTALS IN	URINE	Drain 1	Drain 2	Vomit / Aspirate	Bowels / Stoma / Other	TOTALS OUT	Initials
01:00													
02:00													
03:00													
04:00													
05:00													
06:00													
6 hr CUMULATIVE													
07:00													
08:00													
09:00													
10:00													
11:00													
12:00													
12 hr CUMULATIVE													
13:00													
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18:00													
18 hr CUMULATIVE													
19:00													
20:00													
21:00													
22:00													
23:00													
00:00													
24 hr CUMULATIVE													

24 hr INPUT MINUS OUTPUT - CUMULATIVE BALANCE:

Fig. 5.2: Example of a fluid balance charts which promotes the cumulative measurement of fluid input and output over 6-hour time intervals. This approach promotes earlier identification of patients at risk of developing hypovolaemia or hypervolaemia.

These provide useful information about changes in urine output and abnormal losses, e.g. gastric aspirate, but they have inherent inaccuracies. With great care in measurement and recording, they may be helpful in assessing fluid balance over 24 hours. However, an assumption has to be made concerning insensible loss, and errors in measurement and recording are common. The cumulative error over several days can, therefore, be considerable. A suggested format for fluid balance charts is shown in **Fig. 5.2**.

Weight

There is no substitute for daily weighing as an accurate measure of external water balance. Yet, this is seldom practised outside renal units. As it is a major safeguard against clinically important errors in fluid volume administration, it is worth the extra effort and resources required, particularly in complex postoperative cases. It does, of course, only measure external balance, which may conceal significant changes in internal balance between fluid compartments (e.g. in the presence of ileus or intestinal obstruction large volumes of extracellular fluid may be pooled in the gut and, therefore, be functionally inert). Weight is, therefore, unchanged despite this clinically important fluid shift, which reduces effective ECF volume and necessitates salt and water replacement. Like any other parameter, weight measurements require intelligent interpretation in their clinical context and in the light of all the other information available.

Non-invasive monitoring

Non-invasive assessment of the intravascular volume status can be performed using point of care ultrasound. It can also be used to assess a patient's response to intravenous fluid therapy by measuring the size and respiratory change in the diameter of the inferior vena cava. Ultrasound examination of the lungs can be useful in demonstrating the presence of pulmonary oedema.

Invasive monitoring

Invasive techniques such as insertion of central venous catheters, arterial lines, flow-guided monitoring (e.g. transoesophageal Doppler, Lithium Dilution Cardiac Output [LiDCO], plethysmography or Photonic Integrated Circuits Using Crystal Optics [PICCO]) to measure cardiovascular parameters are useful to help direct fluid therapy in more complex patients[48,49]. These methods are for the expert rather than the novice.

Laboratory tests

Haematocrit

The haematocrit (Hct) is a measurement of the proportion of blood that is made up of cells. Changes in fluid balance can cause an increase or decrease in the concentration of red cells, e.g. in the acute phase of burn injury, plasma loss may be monitored by frequent haematocrit measurements which, therefore, help to guide fluid replacement. Loss of ECF due to gastroenteritis or other causes similarly increases haematocrit. Conversely fluid overload causes a fall in haematocrit due to dilution[50,51].

Haemoglobin

This is expressed as g/L of whole blood (**Table 5.2**). Like the haematocrit, it is elevated in polycythaemia and in fluid depletion. It is reduced in anaemia of any cause and following haemorrhage once the compensatory expansion of plasma volume has occurred. Infusion of intravenous fluid boluses can also cause a fall in haemoglobin as well as haematocrit[50,51].

Albumin

In response to fluid deficit or excess the albumin concentration behaves in the same way as the haematocrit. Indeed, dilution by infused crystalloids is one of the main causes of hypoalbuminaemia in surgical patients[50,51]. Another major cause is the increased albumin escape rate from the circulation in response to proinflammatory cytokines[7] (see **Chapter 1**).

Sodium

This is expressed as a concentration, i.e. the proportion of sodium to water in the ECF. It is not a measure of the absolute amount of sodium in the body or the need for a higher or lower intake. In fact, the commonest cause of hyponatraemia is dilution by overenthusiastic administration of hypotonic fluids (e.g. 5% dextrose or 0.18% saline in 4% dextrose). If, however, water balance is known from daily weighing, then changes in plasma sodium can usually be interpreted in terms of sodium balance. For example, if weight is unchanged, a fall in plasma sodium usually implies that sodium balance is negative and that intake should be increased in the next prescription. On the other hand, if weight has increased by 2 kg and the plasma sodium has fallen, the balance of water is positive and hyponatraemia is dilutional. The next prescription should, therefore, include less water and the same sodium intake as before.

An alternative approach to sodium balance is to measure intake and the sodium content of all fluids lost. This, however, is difficult to do accurately and is more demanding on staff time and resources.

A falsely low serum sodium concentration may be caused by hypertriglyceridaemia, since triglycerides expand the plasma volume but contain no sodium. Similarly, hyponatraemia occurs in the presence of hyperglycaemia as in decompensated diabetes, since glucose also acts as an osmotic agent holding water in the ECF. This effect disappears as soon as insulin treatment causes cellular uptake of glucose and lowering of its concentration in the blood.

Potassium

The normal serum potassium concentration lies between 3.5 and 5.3 mmol/L. Concentrations rising above 5.5 mmol/L increase the risk of death from cardiac arrest and require urgent treatment which may include extra fluids, intravenous glucose and insulin, bicarbonate, calcium gluconate (to stabilise the myocardium), intrarectal calcium resonium and even renal replacement therapy. Conversely, concentrations below 3.0 mmol/L increase the risk of arrhythmias and indicate the need for potassium supplementation by the oral or intravenous route (see **Chapter 14**).

Chloride

Despite the fact that serum chloride measurements do not increase the cost of biochemical screening, many laboratories do not report serum chloride concentrations. However, in the differential diagnosis of acidosis, particularly in patients receiving 0.9% saline (with its high chloride content in relation to plasma)[50-52], it is important for the detection of hyperchloraemic acidosis, in which the serum chloride is elevated and bicarbonate reduced. Hypochloraemic alkalosis may occur due to chloride losses from vomiting and in patients with high nasogastric tube aspirates.

Bicarbonate

Venous or arterial bicarbonate concentrations indicate acid-base status as described in **Chapter 4**.

Table 5.2: Reference laboratory values for some commonly measured blood parameters.

	Normal range
Haemoglobin (g/L)	130-180 (men) 115-165 (women)
Haematocrit (%)	40-54 (men) 37-47 (women)
Na^+ (mmol/L)	135-145
Cl^- (mmol/L)	95-105
$[Na^+]:[Cl^-]$ ratio	1.28-1.45:1
K^+ (mmol/L)	3.5-5.3
HCO_3^- (mmol/L)	24-32
Total Ca^{2+} (mmol/L)	2.2-2.6
Ionised Ca^{2+} (mmol/L)	1.1-1.4
Adjusted Ca^{2+} (mmol/L) (adjusted for albumin)	2.2-2.6
Mg^{2+} (mmol/L)	0.8-1.2
Glucose (mmol/L)	3.5-5.5
Urea (mmol/L)	2.5-6.7
Creatinine (µmol/L)	60-120
eGFR (ml/min/1.73m^2)	>60 without other evidence of kidney disease
pH	7.35-7.45
PaO_2 (kPa)	11-13
$PaCO_2$ (kPa)	4.7-5.9
Lactate (mmol/L)	0.6-1.8
Albumin (g/L)	33-55
Osmolality (mOsm/kg)	275-295

Urea

With renal impairment due to either fluid deficit (pre-renal AKI) or intrinsic tubular AKI, blood urea concentration rises, the rate of increase being greater in the presence of post injury catabolism. Urine output measurements are important but are subject to misinterpretation unless other parameters are also considered. It is useful to combine measurement of urine volume with plasma and urinary urea or osmolality to assess renal function. The urine:plasma urea ratio has been used in the past to measure renal concentrating function and in normal health can be as high as 100 in the presence of dehydration. With a rising blood urea and creatinine, accompanied by oliguria, urine:plasma urea ratio of <15 can be helpful in defining the transition from pre-renal to intrinsic tubular AKI.

Creatinine

Creatinine is a breakdown product generated from normal muscle metabolism and from meat protein in the diet. Therefore, a 120 kg muscular man will generate more creatinine than a 70 kg elderly man. The kidneys filter and secrete creatinine from the blood into the urine at a constant rate. The concentration of serum creatinine, therefore, is inversely proportional to renal function, and rises in the presence of AKI. However, the serum creatinine does not usually rise above the lower limit of normal until the GFR has fallen by 50%. Increases in creatinine are used to define and stage AKI. The majority of hospitals in the UK have adopted an AKI warning system based on a modified algorithm of the KDIGO AKI definition and staging classification[38]. The AKI warning is triggered in any patient who has two serum creatinine concentrations that demonstrate a rise in the creatinine consistent with the definition of AKI (see **Chapter 10**).

Glomerular filtration rate

Glomerular filtration rate (GFR) is the flow rate of filtered fluid through the kidneys and is approximately 120-130 ml/min/1.73 m^2, which equates to the daily filtration of 170-180 litres of water and unbound small molecular weight constituents of blood. It is the most accurate measure of renal function. In reality the measurement of the true GFR is time consuming and requires the administration of radionuclides. It is, therefore, rarely measured except in the assessment of renal function in potential live kidney donors. In every day clinical practice serum creatinine and estimated GFR (eGFR) are used to estimate renal function.

Creatinine clearance

Creatinine clearance provides an estimate of the GFR. The calculation of the creatinine clearance requires a 24-hour urine collection and the measurement of creatinine in the blood and urine. It is now rarely used in clinical practice and the eGFR is used instead.

Cockroft and Gault equation

The Cockcroft-Gault equation[53] provides an estimate of creatinine clearance. This formula is not adjusted for body surface area and may be less accurate in obese patients. The Cockroft-Gault equation overestimates creatinine clearance by approximately 10 to 30%.

$$Creatinine\ Clearance = \frac{(140 - age) \times weight}{(72 \times SCr \times 0.85\ (if\ female)}$$

Age in years, weight in kg and serum creatinine (SCr) in mg/dl

Estimated glomerular filtration rate (eGFR)

The eGFR is commonly calculated from the modified diet in renal diseases (MDRD) formula[54] based on age, sex and serum creatinine concentration. It is a good estimate of renal function in the steady state, but should not be used to estimate kidney function in the setting of AKI. The eGFR value approximates to the percentage of kidney function (e.g. an eGFR of 60 ml/min/1.73 m^2 would approximate to 60% kidney function). It is used to stage CKD and is not validated in patients less than 18 years of age, in pregnancy or obesity or in very muscular patients.

Osmolality

Urinary osmolality >500 mOsm/kg is indicative of pre-renal AKI and <350 mOsm/kg suggests intrinsic tubular AKI. Urinary and serum osmolalities are also used in the diagnosis and monitoring of diabetes insipidus and in the monitoring of hyper- and hypo-osmolal states. This ensures that treatment is controlled carefully to avoid too rapid changes in serum osmolality and consequent risks of central nervous system damage.

Serial data charts

The sticking of individual reports in the back of notes makes it difficult to detect clinically important trends. The only satisfactory way of monitoring patients with fluid and electrolyte problems is the use of serial data charts (**Fig. 5.3**) on which important data are recorded daily, so that changes and trends can be seen at a glance. In our own practice we used to record daily weight, serum biochemistry, haematology, etc. on charts which were kept by the patient's bedside. However, this information is now stored in the digital patient record from which it can be retrieved easily.

Date	Na	K	Urea	Creat	eGFR	AKI
08-Aug-2021	140	3.6	6.3	70	70	
07-Aug-2021	**147**	4.3	**8.7**	71	69	
06-Aug-2021	**156**	3.6	**13.6**	83	58	
05-Aug-2021	**158**	**3.3**	**17.5**	83	58	
04-Aug-2021	**164**	4.4	**34.0**	**147**	30	**2**
03-Aug-2021	**164**	4.8	**33.7**	**155**	28	**2**
02-Aug-2021	**167**	4.0	**22.9**	**111**	41	**1**

Fig. 5.3: An example of an electronic chart with serial blood results. This patient presented with hypernatraemia and acute kidney injury due to dehydration. It can be seen from the AKI column that the patient developed AKI stage 2. With appropriate treatment the sodium and creatinine improved to within the normal range.

Chapter 6:
PROPERTIES OF INTRAVENOUS CRYSTALLOIDS AND COLLOIDS

A variety of crystalloids containing salt and/or glucose and of artificial colloids is available for use in intravenous fluid therapy.

To expand the intravascular volume during resuscitation current practice is to use a combination of salt containing crystalloids (preferable balanced electrolyte solutions) and colloids (the use of hydroxyethyl starch is discouraged for critically ill patients and those with sepsis and burns in most European countries because of possible renal toxicity). The properties of some commonly used crystalloids are summarised in **Table 6.1** and must be borne in mind when choosing the most appropriate fluid for any particular situation.

The ability of a solution to expand the plasma volume is dependent on its volume of distribution and the metabolic fate of the solute, so that while colloids are mainly distributed in the intravascular compartment, dextrose containing solutions, once the dextrose is metabolised, are distributed through the total body water and hence have a very limited and transient capacity to expand the blood volume (**Fig. 6.1**, **Table 6.2**). Solutions like 5% dextrose and dextrose saline are not meant for resuscitation, but are a means of providing free water when this is appropriate.

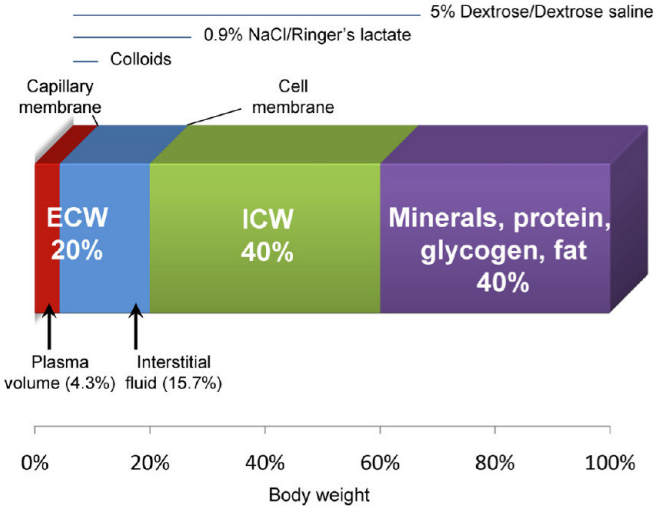


Fig. 6.1: Distribution of fluids through the body water compartments. About 20-25% of isotonic crystalloids and 50-70% of colloids remain in the intravascular compartment while the remainder enters the interstitial space. Solutions like 5% dextrose provide free water and are distributed throughout the total body water.

Table 6.1: Properties of commonly prescribed crystalloids.

	Plasma*	0.9% NaCl	Hartmann's	Lactated Ringer's (USP)	Ringer's acetate	Plasma-Lyte 148	Sterofundin ISO	0.18% NaCl /4% dextrose	Plasma-Lyte 56 Maintenance	0.45% saline	5% dextrose
Na^+ (mmol/L)	135-145	154	131	130	130	140	145	31	40	77	0
Cl^- (mmol/L)	95-105	154	111	109	112	98	127	31	40	77	0
$[Na^+]:[Cl^-]$ ratio	1.28-1.45:1	1:1	1.18:1	1.19:1	1.16:1	1.43:1	1.14:1	1:1	1:1	1:1	-
K^+ (mmol/L)	3.5-5.3	0	5	4	5	5	4	0	13	0	0
HCO_3^-/ Bicarbonate precursor (mmol/L)	24-32	0	29 (lactate)	28 (lactate)	27 (lactate)	27 (acetate) 23 (gluconate)	24 5 (malate)	0	16	0	0
Ca^{2+} (mmol/L)	2.2-2.6	0	4	1.4	1.0	0	2.5	0	2.5	0	0
Mg^{2+} (mmol/L)	0.8-1.2	0	0	0	1	1.5	1.0	0	1.5	0	0
Glucose (mmol/L)	3.5-5.5	0	0	0	0	0	0	222.2 (40 g)	277.8	0	277.8 (50 g)
pH	7.35-7.45	4.5-7.0	5.0-7.0	6.0-7.5	6.0-8.0	4.0-8.0	5.1-5.9	4.5	3.5-6.0	4.5-7.0	3.5-5.5
Osmolarity (mOsm/L)	275-295	308	278	273	276	295	309	284	389	154	278

**Normal laboratory range from Nottingham University Hospitals, Nottingham*

Table 6.2: Volume of infusion required to expand the plasma volume by 1 L.

	Infused volume (mL)	Change in interstitial fluid (mL)	Change in intracellular fluid (mL)
5% albumin	1400-1500	400-500	
25% albumin	250	-750*	
6% hydroxyethyl starch	1400-1500	400-500	
Succinylated gelatin	1400-1600	400-600	
Hartmann's solution or 0.9% saline	4000-5000	3000-4000	
5% dextrose	14000	3000-4000	9000-10000

** Fluid is drawn into the intravascular compartment from the interstitial compartment*

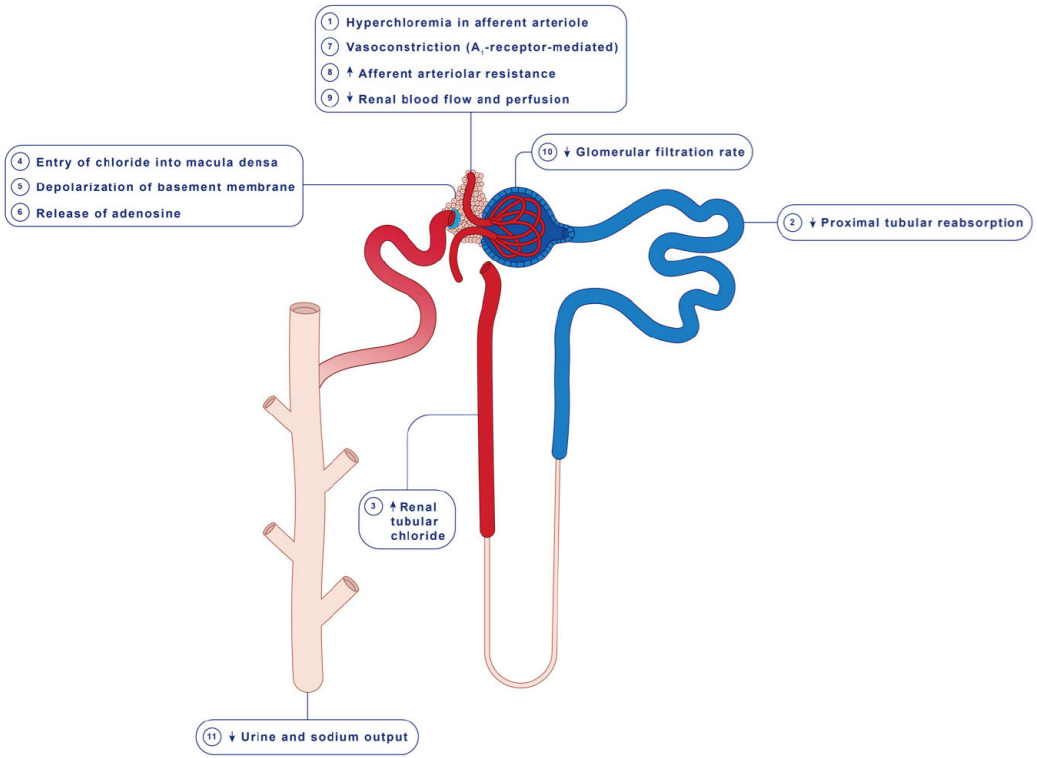


Fig. 6.2: Hyperchloraemia and the kidney (Modified and redrawn from Lobo and Awad[55]).

Isotonic sodium-containing crystalloids are distributed throughout the ECF (including the plasma) and classical textbook teaching suggests that such infusions expand the blood volume by a third of the volume of crystalloid infused. In practice, however, the capacity of these solutions to expand the plasma volume is only 20-25% of the volume infused, the remainder being sequestered in the interstitial space. Although these solutions are used successfully for this purpose, the price paid for adequate intravascular filling is overexpansion of the interstitial space and tissue oedema. This residual excess of salt and water has then to be excreted once the acute phase of illness has passed (see **Chapter 13**). Solutions of dextrose or of hypotonic saline can cause significant hyponatraemia (Na^+ <130 mmol/L), and care should be taken to avoid this potentially harmful effect, particularly in children and the elderly. Compared with balanced crystalloids, 0.9% saline produces a hyperchloraemic acidosis because of its high chloride content compared with plasma (**Table 6.1**). This causes a reduction in the strong ion difference ($[Na^+] + [K^+] – [Cl^-]$) and also results in reduced renal blood flow and glomerular filtration (**Fig. 6.2**)[56], as well as gastrointestinal mucosal acidosis and ileus, cellular dysfunction, impairment in mitochondrial function, oedema and worse outcome[55,57]. These effects are described in more detail in **Chapter 16**. For these reasons balanced electrolyte solutions are preferred to 0.9% saline in most instances, unless there is chloride deficiency (e.g. from vomiting or gastric aspiration)[55].

Colloids are homogenous non-crystalline large molecules or ultramicroscopic particles dispersed through a fluid, usually a crystalloid. Colloidal particles are large enough to be retained within the circulation and, therefore, to exert an oncotic pressure across the capillary membrane. The ideal colloid should be readily available, have a long shelf life, have no special infusion or storage requirements and be relatively inexpensive. It should be suspended in an isotonic solution, have a low viscosity, be iso-oncotic with plasma and be distributed exclusively in the intravascular compartment, with a half-life of 6-12 h. The colloid should be metabolised or excreted and should not accumulate in the body. It should not be toxic, pyrogenic, allergenic or antigenic and should not interfere with organ function (e.g. renal or coagulation) or with acid base balance. There is no ideal colloid, that completely fulfils all these criteria, and the colloids used for volume replacement are either naturally occurring (human albumin solution, plasma protein fraction, fresh frozen plasma, and immunoglobulin solutions) or semisynthetic (gelatins, starches and dextrans). In the UK, commonly used colloids include succinylated gelatin (e.g. Gelofusine), urea-linked gelatin (e.g. Haemaccel) and albumin (for selected indications). Older preparations of hydroxyethyl starch are suspended in 0.9% saline while the newer preparations (Volulyte, Tetraspan) and gelatins (Gelofusine, Gelaspan and Haemaccel) are suspended in solutions containing lower amounts of chloride, making them more physiological. All currently available semisynthetic colloids contain 140-154 mmol Na^+ and therefore, contribute to the positive sodium balance seen in surgical patients.

Recent large randomized controlled trials have demonstrated that, in critically ill or septic patients, hydroxyethyl starch has an adverse effect on renal function, and in some cases on mortality, when compared with crystalloids[58-60]. The Pharmacovigilence Risk Assessment Committee of the European Medicines Agency considered this evidence and initially issued cautionary guidance on the use of hydroxyethyl starch[61]. In January 2018, PRAC recommended suspending the marketing authorisations of hydroxyethyl starches. However, in July 2018, a controlled access programme was implemented to ensure that only accredited hospitals will be supplied with these medicines. This accreditation would require that relevant healthcare professionals receive training on the safe use of hydroxyethyl starches[61]. Albumin solutions are monodisperse as they contain particles of uniform molecular weight (69 kD) while

synthetic colloids contain particles of varying sizes and molecular weights in an attempt to optimise the half-life (which is directly proportional to particle size) and plasma volume expanding capacity (which is proportional to the number of particles suspended) of the solutions.

With the moratorium on hydroxyethyl starches, albumin is now being used for resuscitation, especially in patients with sepsis[62]. Concentrated (20-25%) salt poor albumin may also be useful in patients in the post-acute phase of illness who are oedematous due to salt and water overload, but who still have a plasma volume deficit, as it helps draw fluid from the interstitial space into the intravascular space and improves renal perfusion allowing excretion of excess salt and water[63]. Albumin is also used in patients with hepatic failure and ascites[64]. However, the prescription of this expensive preparation should be confined to senior clinicians.

Although, in theory, those colloids that are isooncotic with plasma should expand the blood volume by the volume infused, in practice, their volume expanding capacity is only 60-80%. Nevertheless, a given volume of colloid results in greater volume expansion and less interstitial oedema than an equivalent volume of crystalloid (**Table 6.3**). The advantages and disadvantages of colloids are summarised in **Table 6.4**. Although, in practice in the UK, we use a combination of crystalloids and colloids for resuscitation, there is, in fact, no firm evidence that the use of colloids rather than crystalloids in the acute phase of injury results in better outcome.

Table 6.3: Volume effects of some colloidal solutions.

Colloidal solution	Duration of action	Initial plasma expanding effect (%)
Long acting	5-6 h	
6% HES 450/0.7		100
6% HES 200/0.62		100
Medium acting	3-4 h	
6% HES 130/0.4		100
4% gelatins		130
Short acting	1-2 h	
6% HES 70/0.5		70
3% gelatin		70
5% albumin		70-90

HES=hydroxyl ethyl starch. Properties are dependent on concentration, the weight-averaged mean molecular weight (Mw), the number-averaged molecular weight (Mn), the molar substitution (MS) and the degree of substitution.

Table 6.4: Advantages and disadvantages of colloids.

Advantages	Disadvantages
Smaller volumes than crystalloids are needed for plasma volume expansion	Allergic reactions/anaphylaxis [<0.4% - less for albumin (0.1%) and hydroxyethyl starch (0.06%)]
Less oedema produced than with crystalloids	Renal toxicity (hydroxyethyl starch)
Potential free radical scavenging effect (especially albumin)	Coagulopathy
	Pruritus
	May interfere with blood cross-matching

Conclusion

There are good theoretical grounds for using colloids for plasma volume expansion as they cause less salt and water overload and oedema than crystalloids. In practice, however, we tend to use a combination of the two in varying proportion according to the circumstances. There are very few indications for using 0.9% saline (except in cases of chloride deficiency, e.g. from vomiting) and balanced crystalloids are preferred in most circumstances. Although hydroxyethyl starch is still being used in some countries, its use in Europe has been recommended with caution by European Medicines Agency because of reports of renal toxicity[61]. The colloids currently in use in Europe include albumin and gelatins.

Chapter 7: PRESCRIPTION AND ADMINISTRATION

Fluid and electrolytes may be administered orally, enterally, subcutaneously, or intravenously (peripherally or centrally), depending on the clinical situation. Before any prescription is written it is important to ask a number of questions:

Question 1. Does the patient need any prescription at all today?
If the patient is eating and drinking, the answer is usually no. In the case of a postoperative patient, for example, any intravenous fluids should be discontinued as soon as possible. Intravenous fluids are often continued unnecessarily, leading to fluid overload as well as increased risk of cannula-site thrombophlebitis and infection. Nasogastric tubes are only indicated for drainage in the presence of true ileus or gastric dysfunction (e.g. delayed gastric emptying after pancreatic surgery). In the majority of cases, morbidity from nasogastric tubes exceeds any benefit. Gastrointestinal function returns more rapidly postoperatively than assumed previously. The absence of bowel sounds *per se* does not mean that food and drink will not be tolerated. In the past, a combination of nasogastric tubes and excess intravenous fluids has frequently caused unnecessary delay in re-establishing oral intake, increased risk of complications and a prolonged length of stay[57,65,66].

Patients receiving artificial nutrition (parenteral or enteral) usually receive an adequate amount of water and electrolytes via the feed and most do not require additional intravenous fluids. It is a common mistake to prescribe intravenous maintenance requirements in addition to the water and electrolyte content of the feed, leading to avoidable fluid overload.

Question 2. If so, does the patient need this for

a. resuscitation,
b. replacement of losses, or
c. merely for maintenance?

This question is crucial. Many patients are fluid overloaded because prescriptions based on resuscitation are continued thoughtlessly when maintenance fluids are all that is required. **Tables 1.1** and **1.2** show how low such maintenance requirements are. For example, 1 litre of 0.9% saline contains enough salt to meet 2 days' normal maintenance requirements for sodium. Intravenous fluid therapy may be needed for resuscitation, replacement or maintenance, depending on the stage of the illness (**Fig. 7.1**).

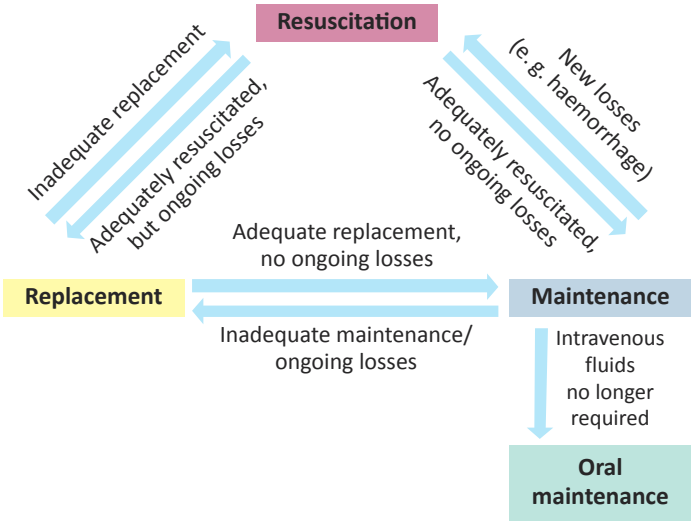


Fig. 7.1: Indications for intravenous fluid therapy and the relationship between resuscitation, replacement and maintenance.

Resuscitation: In the event of blood loss from injury or surgery, plasma loss e.g. from burns or acute pancreatitis, or gastrointestinal or renal losses of salt and water, a resuscitation regimen is needed to restore and maintain the circulation, tissue perfusion and the function of vital organs. In this situation, patients should receive a rapid infusion of 500 ml (250 ml if risk of cardiac failure) of a balanced crystalloid (e.g. Hartmann's solution, Ringer's lactate, Plasmalyte 148 or Sterofundin). Two randomised trials have shown that if the initial resuscitation of patients in the emergency department was performed with balanced crystalloids, the incidence of major adverse kidney events was significantly lower than if resuscitation was performed with 0.9 saline in both critically ill patients[67] and those who were not critically ill[68]. If hyperkalaemia is present (K^+ >5.5 mmol/L) or suspected oliguric AKI or rhabdomyolysis 0.9% saline is preferred initially (no potassium in this crystalloid). However, there is no evidence that administration of crystalloids containing 3-5 mmol/L of potassium worsen the hyperkalaemia[69,70]. The clinical response should be assessed immediately following administration of the fluid bolus in terms of improved peripheral perfusion, decreased pulse rate, rise in blood pressure, rise in JVP and increase in urine output. Further administration will depend on the response (**Fig. 7.2**). If 0.9% saline has been used initially, conversion to a balanced crystalloid can be considered once potassium concentrations are known and good urine output has been established.

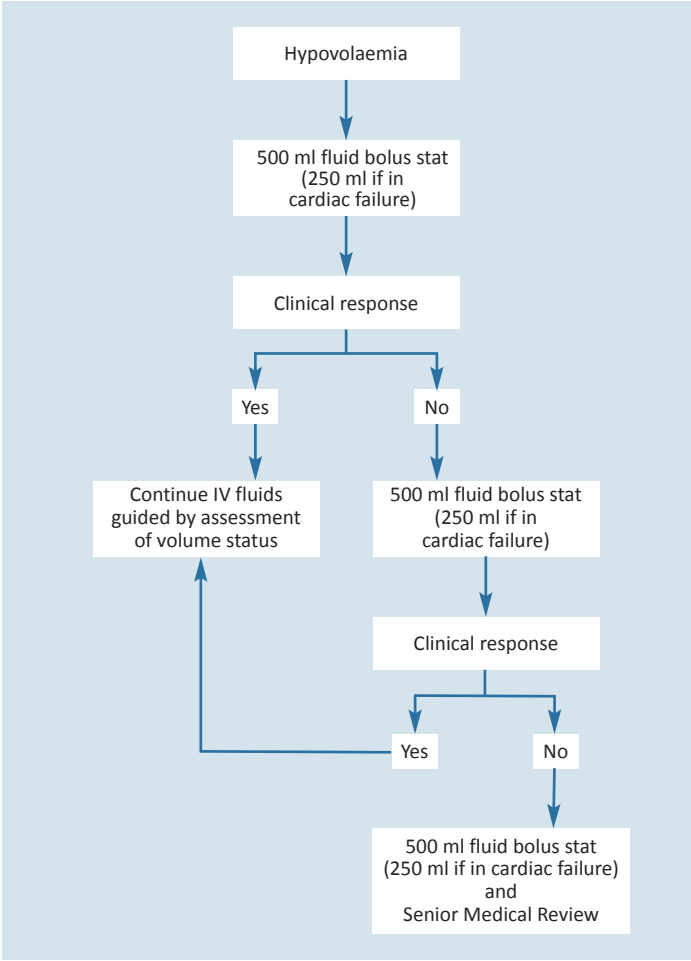


Fig. 7.2: Suggested algorithm for resuscitation of acute non-haemorrhagic fluid depletion.

In the case of intravascular fluid losses, colloids or a combination of colloids and crystalloids may be appropriate. However, in the light of reports of adverse events caused by infusion of hydroxyethyl starch in critically ill patients[58-60], the Pharmacovigilence Risk Assessment Committee of the European Medicines Agency (EMA)[61] made the following recommendations about the use of hydroxyethyl starches:

- They are contraindicated in patients with sepsis, burns or critical illness.
- They should only be used for the treatment of hypovolaemia caused by acute blood loss when crystalloids alone are not considered sufficient.
- They should be used at the lowest effective dose for the shortest period of time.
- They should not be used for more than 24 h and patients' kidney function should be monitored for 90 days.

However, this guidance has now been changed and the recommendation is to use hydroxyethyl starches with caution in accredited hospitals[61]. Albumin solutions may be of benefit when used to resuscitate patients with sepsis. Gelatins are used frequently, but the risk of anaphylaxis is greater with gelatins than starches.

Large volumes of 0.9% saline are best avoided, except after gastric losses, because of the risk of producing hyperchloraemic acidosis and its undesirable sequelae[55]. In the case of major blood loss it is also necessary to cross match and to give packed cells. Early and adequate treatment of the underlying cause of fluid loss, e.g. control of bleeding, is vital. In the severely injured patient, replacement of blood loss with packed cells, fresh frozen plasma and platelets in a ratio of 1:1:1 has been shown to be more beneficial than packed cells alone, as this helps correct the associated coagulation defects[71].

Algorithms for the initial resuscitation of the patient in haemorrhagic shock, as recommended by the Committee on Trauma of the American College of Surgeons[72] and the patient in septic shock, as recommended by the Surviving Sepsis Campaign[40] are shown in **Figs. 7.3** and **7.4** respectively. It must be remembered that these are complex situations and senior help should be sought as soon as possible. Further details for management of the patient with haemorrhagic shock can be accessed from the Advanced Trauma Life Support® Manual[72] and for the patient with sepsis from the Guidelines of the Surviving Sepsis Campaign[40].

Recognise the presence of haemorrhagic shock
Definitive control of haemorrhage and restoration of adequate circulating volume are the goals of treating haemorrhagic shock.
The most effective method of restoring adequate cardiac output, organ perfusion, and tissue oxygenation is to restore venous return to normal by stopping bleeding. Volume repletion will allow recovery from shock only when bleeding has stopped.
Establishing a patent airway with adequate ventilation and oxygenation is the first priority. Supplementary oxygen should be given to maintain oxygen saturation at >9S%.
In unconscious patients, gastric distention increases the risk of aspiration of gastric contents, a potentially fatal complication. Insert a nasogastric tube
Administer an initial, warmed fluid bolus of isotonic fluid. The usual initial dose is 1 L for adults. Further volumes of fluid should be based on the response to fluid resuscitation
Early administration of blood products at a low ratio of packed red blood cells to plasma and platelets can prevent the development of coagulopathy and thrombocytopenia.
Work in a team and call for senior help

Fig. 7.3: Initial resuscitation for the patient with haemorrhagic shock[72].

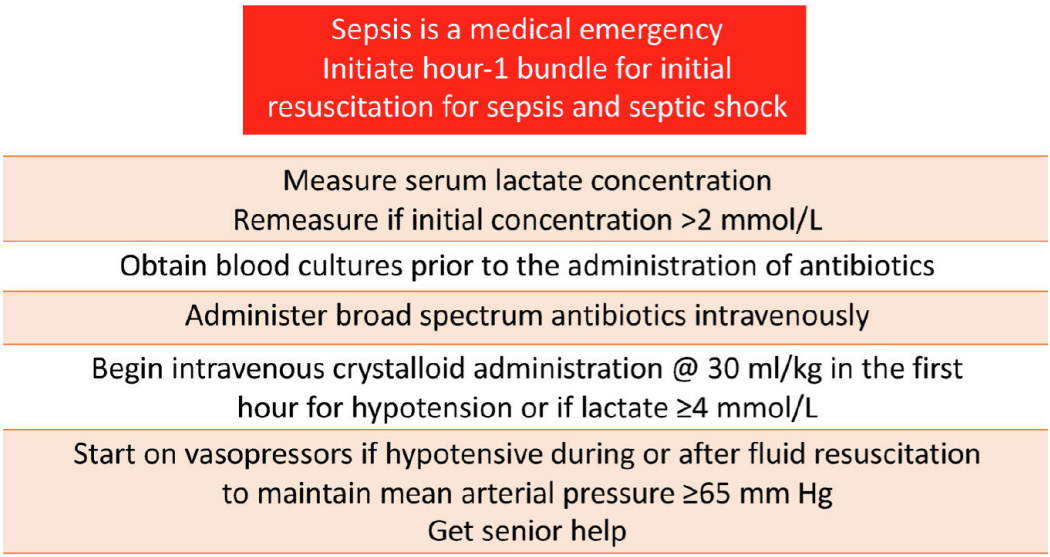


Fig. 7.4: First hour resuscitation bundle for the patient with sepsis/septic shock. Data from Evans et al.[40].

Once resuscitation has been achieved as judged by normalisation of vital signs and urine output or of parameters from more invasive measurements, the prescriber should switch to a maintenance regimen with accurate replacement of any continuing losses. Exceeding such requirements, in the mistaken belief that the patient will excrete any excess, delays recovery and impairs outcome.

Replacement: Any fluid prescription should incorporate not only daily maintenance requirements, but replacement of any ongoing abnormal losses. In the case of a patient with losses from any particular part of the gastrointestinal tract (e.g. from a fistula), the fluid prescription should include the daily maintenance requirements plus like-for-like water and electrolyte replacement of any losses. In order to achieve this, the prescriber should be aware of the approximate electrolyte content of fluid at different levels of the gastrointestinal tract (see **Table 1.3**).

Maintenance: Maintenance prescriptions should aim to replace insensible loss (500-1000 ml), provide sufficient water and electrolytes to maintain the normal status of body fluid compartments, and sufficient water to enable the kidney to excrete waste products 500-1500 ml (**Tables 1.2** and **1.3**). The average person requires 25-30 ml/kg water, 1 mmol/kg sodium and 1 mmol/kg potassium per day. Examples of how to provide this maintenance requirement are summarised in **Table 7.1**. Some drugs contain appreciable amounts of sodium, especially if diluted and administered in 0.9% saline (see **Chapter 6**). This additional sodium load should be taken into account when planning fluid prescriptions. **Table 7.2** gives some examples of the sodium content of drugs, but is not comprehensive. If in doubt, the hospital pharmacist should be consulted.

Question 3. What is the patient's current fluid and electrolyte status and what is the best estimate of any current abnormality?

The answer to this question is summarised in **Chapter 5**. Decision making should be achieved by using all the information available, including history, examination, vital signs, measurements and tests including urine output and concentration and serum biochemistry, fluid balance charts, weight changes, and an understanding of the likely pathophysiological changes. It should not be based just on casual bedside assessment of unreliable and non-specific signs such as dry mouth or diminished skin turgor. Remember, serial weighing is the most accurate measure of external water balance.

Table 7.1: Some examples of maintenance fluid regimens (2-2.5 L/day) suitable for a 70 kg person.

	0.18% saline in 4% dextrose (2-2.5 L)	**0.45% saline (1-1.5 L) + 5% dextrose (1 L)**	**Plasma-Lyte 56 Maintenance**	**Plasma-Lyte 148 (1 L) + 5% dextrose (1-1.5 L)**	**Ringer's lactate (1 L) + 5% dextrose (1-1.5 L)**	**Hartmann's (1 L) + 5% dextrose (1-1.5 L)**	**Sterofundin ISO (1 L) + 5% dextrose (1-1.5 L)**
Water (L)	2-2.5	2-2.5	2-2.5	2-2.5	2-2.5	2-2.5	2-2.5
Na^+ (mmol)	60-75	77-116	80-100	140	130	131	145
Cl^- (mmol)	60-75	77-116	80-100	98	109	111	127
K^+ (mmol)	Should be added	Should be added	26-33 (Extra K^+, if needed, should be added to 5 % dextrose)	5 (Extra K^+ should be added to the 5 % dextrose)	4 (Extra K^+ should be added to the 5 % dextrose)	5 (Extra K^+ should be added to the 5 % dextrose)	4 (Extra K^+ should be added to the 5 % dextrose)
Dextrose (g)	80-100	50	100-125	50-75	50-75	50-75	50-75
Ca^{2+} (mmol)					1.4	2	2.5
Lactate (mmol)					28	29	
Acetate (mmol)			32-40	27			24
Gluconate (mmol)				23			
Malate (mmol)							5
Mg^{2+} (mmol)			3-4.5	1.5			

Table 7.2: Sodium content of some drugs.

Drug and dosage	Sodium content (mg)	Sodium content (mmol)
Acyclovir 1 g	96.6	4.2
Amikacin sulphate 1 g	29.9	1.3
Ampicillin 1 g	66.7	3
Cephazolin sodium 1 g	47	2
Ceftazidine 1 g	54	2.3
Ceftriaxone sodium 1 g	59.8	2.6
Cefuroxime 1 g	55.2	2.4
Erythromycin ethylsuccinate suspension 200 mg/5 ml	29	1.3
Imipenum/cilastatin 1 g	73.6	3.2
Metronidazole 500 mg	322	14
Penicillin G potassium 1 million units	7	0.3
Penicillin G sodium 1 million units	46	2
Piperacillin/tazobactam 1 g	54	2.35

Question 4. Which is the simplest, safest, and most effective route of administration?

The most appropriate method of administration should be the simplest and safest that is effective (**Chapter 8**). The oral route should be used whenever possible. In acute situations and in the presence of gastrointestinal dysfunction or large deficits, the intravenous route is the most appropriate. However, intravenous fluid administration should be discontinued at the earliest opportunity. Administration of fluid by enteral tubes may be appropriate where swallowing is the major problem. Subcutaneous infusions (hypodermoclysis)[73] should be considered, particularly in the elderly, for the management of chronic or recurrent problems (see **Chapter 8**).

Question 5. What is the most appropriate fluid to use and how is that fluid distributed in the body?

The most appropriate fluid to use is that which most closely matches any previous or ongoing losses. Recent evidence favours the use of balanced electrolyte solutions rather than 0.9% saline to replace salt and water deficits[55,56], except in the case of losses of gastric juice with its high chloride content. Colloids should be used cautiously and in accordance with the recommendations described above. Blood and blood products should be used appropriately when indicated (see above).

Conclusion

It is important to be clear about the objective of any fluid prescription whether it be resuscitation, replacement or maintenance to avoid giving too little or too much, since both will have an adverse effect on outcome. The distribution of any infused fluid in the body water compartments should be understood and the contribution of any additional electrolyte (e.g. sodium content of drugs) should be taken into account in any calculation of fluid and electrolyte balance. Fluid should be administered in the simplest way possible and intravenous fluids discontinued as soon as adequate oral intake is established.

Chapter 8: ROUTES OF FLUID ADMINISTRATION

ORAL OR ENTERAL

The use of oral rehydration solutions to treat diarrhoeal disease in both children and adults is one of the most commonly used treatments worldwide, particularly in low- and middle-income countries. They can also be useful in the management of short bowel or inflammatory bowel disease in hospital or at home.

These preparations are based on the principle that salt absorption in the small bowel is linked to that of carbohydrate and is, therefore, enhanced by glucose, glucose polymers, and starch (e.g. rice water)[74]. Some preparations also contain potassium and an alkalising agent to counter acidosis. In developing countries, they can be made using locally available materials, with simple measuring devices to ensure the correct proportions of salt, sugar or rice starch, and boiled water. In the UK commercial preparations are available (see British National Formulary), 5 sachets of Dioralyte (Sanofi, Guildford, UK), for example, reconstituted in 1 litre of water, give Na^+ 50 mmol, K^+ 20 mmol, Cl^- 50 mmol, citrate 10 mmol, and glucose 90 mmol. The WHO formula contains 75 mmol/L Na^+. These are suitable for diarrhoeal diseases in children and most adults, although, in short bowel syndrome or inflammatory bowel disease in adults, a more concentrated solution may be required and can be obtained mixing more sachets per litre.

Fluid and electrolytes may also be administered via enteral tubes (nasogastric, percutaneous gastrostomy or jejunostomy) where oral administration is difficult. Monitoring of oral or enteral fluid treatment follows the same general principles as outlined in **Chapter 5**. One of the advantages of oral and enteral over intravenous administration is that, owing to the regulatory mechanisms of the gastrointestinal tract, it is difficult to give excess fluid. On the other hand, when fluid losses are very great, or in the presence of gastrointestinal failure, the intravenous route may be necessary for resuscitation and replacement or to maintain balance.

In patients receiving nutritional support by whatever route, the fluid and electrolyte content of the feed should be included when calculating fluid and electrolyte balance and writing fluid prescriptions.

INTRAVENOUS

Peripheral

Most fluids are infused via a peripheral venous cannula. Such cannulae should be inserted and maintained using meticulous care, technique and protocols, since their potential for causing morbidity and even mortality from infection is often underestimated. Each hospital should have clear guidelines, as part of clinical governance, to ensure optimal care of peripheral cannulae (**Fig. 8.1**). Insertion sites should be inspected daily and cannulae removed or resited at the earliest sign of any inflammation. In any case, it is good policy to resite cannulae at least every 72 h[75].

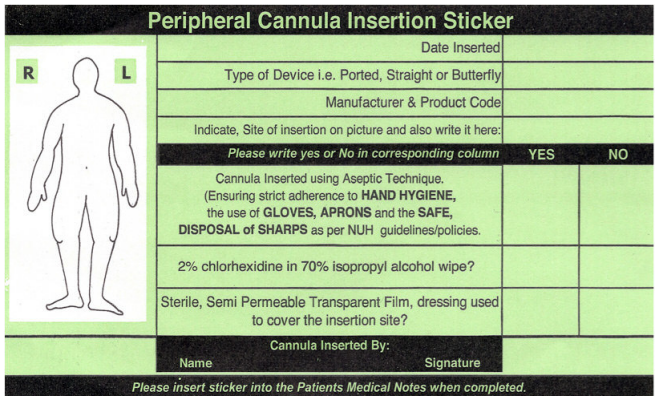


Fig 8.1: Example of a sticker used for peripheral cannula insertion.

Central

Modern single or multi lumen polyurethane or silastic lines inserted via the internal jugular or subclavian vein have even greater potential than peripheral cannulae to cause morbidity and mortality unless inserted and maintained by skilled staff observing standard protocols. Ideally, they should be inserted using ultrasound guidance[76] and strict aseptic precautions should be observed while inserting and using them. Hypertonic glucose solutions or those with high potassium concentrations should be given by the central rather than the peripheral route in order to prevent phlebitis.

SUB-CUTANEOUS ROUTE (HYPODERMOCLYSIS)

This method has been used in paediatrics and health care of the older adult for many years. It is particularly effective for replacing small or medium fluid and electrolyte losses in patients unable to maintain balance by the oral route and deserves wider use. One of its advantages is that patients or their carers can be taught to manage it at home. We have found it particularly useful for domiciliary use in adult and elderly patients with salt and water losses from gastrointestinal diseases[73].

As an example, 0.9% saline (500-2000 ml daily) or 5% dextrose (500 ml) containing up to 20 mmol K^+ and/or 4 mmol Mg^{2+} per litre may be infused over 3-4 hours via a fine butterfly cannula inserted into the subcutaneous fat, usually over the torso.

INTRAOSSEOUS ROUTE

The intraosseous route for fluid infusion directly into the marrow of a long bone has been primarily used as an alternative in children with difficult intravenous access and military combat casualty care. However, in the last two decades, this route has also been established for the resuscitation of adults in emergency situations. The usual sites for insertion of an 18G needle with trocar (or proprietary device) are the anteromedial surface of the proximal tibia, 2-3 cm below the tibial tuberosity; the distal tibia, proximal to the medial malleolus; and the distal femur. Contraindications to the intraosseous route include, among others, proximal ipsilateral fracture, ipsilateral vascular injury and osteogenesis imperfecta. Intraosseous infusion should be limited to emergency resuscitation and discontinued when other venous access has been obtained.

INFUSION PUMPS

When fluid is delivered by either the enteral or parenteral route, what is prescribed is not necessarily what is delivered, and patients may receive either too much or too little as a result of inaccuracies in delivery rates. It is now recommended that fluids should be delivered using infusion pumps set at pre-determined rates (**Table 8.1**), which can be up to 999 ml/h. This increases the accuracy of fluid delivery. Nevertheless, delays in changing fluid bags once they are empty may still lead to errors.

Table 8.1: Setting rates of infusions on pumps.

Rate of infusion	Duration for delivery of 1 litre
41.7 ml/h	24 h
55.6 ml/h	18 h
83.3 ml/h	12 h
100 ml/h	10 h
125 ml/h	8 h
166.7 ml/h	6 h
250 ml/h	4 h
500 ml/h	2 h
999 ml/h	1 h

CONCLUSION

In planning fluid therapy it is important to select the safest, simplest and most appropriate route and to monitor this carefully to avoid over- or under-treatment and any potential complications of the method. The aphorism, 'if the gut works, use it' is as appropriate in fluid therapy as it is in nutritional care.

Chapter 9: OLIGURIA

INTRODUCTION

In health a normal diet generates about 600 mOsm/day of solute waste products that need to be excreted in the urine. With normal renal function and maximal antidiuretic hormone stimulation a minimum urine volume of 500 ml/day is required for this purpose (the volume obligatoire of Claude Bernard)[1,2]. Oliguria is, therefore, defined as a urine output <0.5 ml/kg/h. However, it is important to determine whether it is physiological, i.e. a normal response to surgery/injury or pathological, e.g. secondary to hypovolaemia and/or sepsis, resulting in hypoperfusion of the kidneys and AKI (see **chapter 10**).

PHYSIOLOGICAL OLIGURIA

Oliguria, occurring soon after uncomplicated surgery, is usually part of the normal physiological response to injury (see **Chapter 1**), conserving salt and water in an attempt to maintain intravascular volume. Isolated oliguria in the first 48 hours after uncomplicated surgery, therefore, does not necessarily reflect intravascular hypovolaemia, although it may do so if confirmatory features are present, e.g. tachycardia, hypotension, low central venous pressure (CVP), decreased capillary refill, etc. (**Table 9.1**).

The key clinical question, therefore, is whether or not the oliguria is pathological, i.e. due to significant intravascular hypovolaemia requiring treatment. It is, therefore, essential that the patient's volume status is assessed carefully (**Table 9.1**). Remember that serial changes give more information than single observations. Also remember the importance of charting data in a serial manner and in a way that is easily accessible to the clinician. In difficult cases, particularly intra-operatively, invasive monitoring may be required to guide optimal treatment[77].

Urine output should be interpreted in the light of these clinical signs and measurements before giving fluid treatment, which, in the absence of hypovolaemia, may not only be unnecessary, but also deleterious. Unnecessary fluid therapy not only expands the blood volume excessively but also over-expands the interstitial fluid volume, causing oedema and weight gain. The metabolic response to surgery further impairs the patient's ability to excrete the additional saline load, making interstitial oedema worse and compromising organ function, increasing the risk of morbidity and mortality. Other consequences are dilution of the haematocrit and serum albumin concentration[50,51] (See **Chapter 5**).

Table 9.1: Assessment of volume status.

Capillary refill time	
Pulse rate	• Beta blockers / diltiazem (prevent tachycardia)
Blood pressure	• Lying and standing
Jugular venous pressure	
Skin turgor (over clavicle)	
Auscultation	• Lungs (pulmonary oedema) • Heart sounds (gallop rhythm - hypervolaemia)
Oedema	• Peripheral/sacral
Urine output	
Weight change to assess water balance	

OLIGURIA SECONDARY TO AKI

Although it is important not to give excess fluid, giving too little also has serious consequences[66]. Failure to recognize and treat intravascular hypovolaemia (and pre-renal AKI) adequately may compromise organ perfusion and result in the development of intrinsic AKI. There is evidence that patients with oliguric AKI have more severe tubular damage and a worse outcome.

Once a diagnosis of AKI has been made, the underlying cause must be established (see **Chapter 10**). The most common causes are hypovolaemia and/or sepsis leading to hypoperfusion of the kidneys. Clinical examination must be performed to establish the patient's volume status and the source of sepsis must be identified and treated promptly. If the patient is hypovolaemic, then appropriate fluid therapy must be given according to a documented management plan, which requires regular review and defined endpoints[78,79] (**Fig. 9.1**).

In a patient with hypovolaemia and oliguric AKI

- consider inserting a urinary catheter (not routine and may introduce infection) to aid with the assessment of volume status particularly if the patient is confused or incapacitated due to the severity of the acute illness
- resuscitate with IV fluids (fluid challenge)
  - stat fluid bolus of 500 ml (250 ml if in cardiac failure) of balanced crystalloid (0.9% saline if hyperkalaemic) or colloid
- assess clinical response to fluid in terms of
  - capillary refill time
  - pulse (reduction in pulse rate if tachycardic)
  - jugular venous pressure (rise in JVP)
  - blood pressure (rise in BP)
  - pulmonary oedema (if present stop iv fluids)
  - urine output
- if there is a clinical response to a fluid bolus, continue with replacement fluids and discuss further fluid therapy plans with a senior member of the team
- if there is no clinical response and no pulmonary oedema, administer a further 500 ml of crystalloid, reassess clinically and discuss with a senior member of the team. Remember to consider the possibility of postoperative bleeding as a cause for the hypovolaemia and failure to respond to a fluid challenge.
- if the patient has volume unresponsive oliguric AKI, continue with iv fluids cautiously, matching urine output and at the same time monitoring for signs of respiratory distress (rising respiratory rate, pulmonary oedema or falling oxygen saturations). Refer to the renal team.

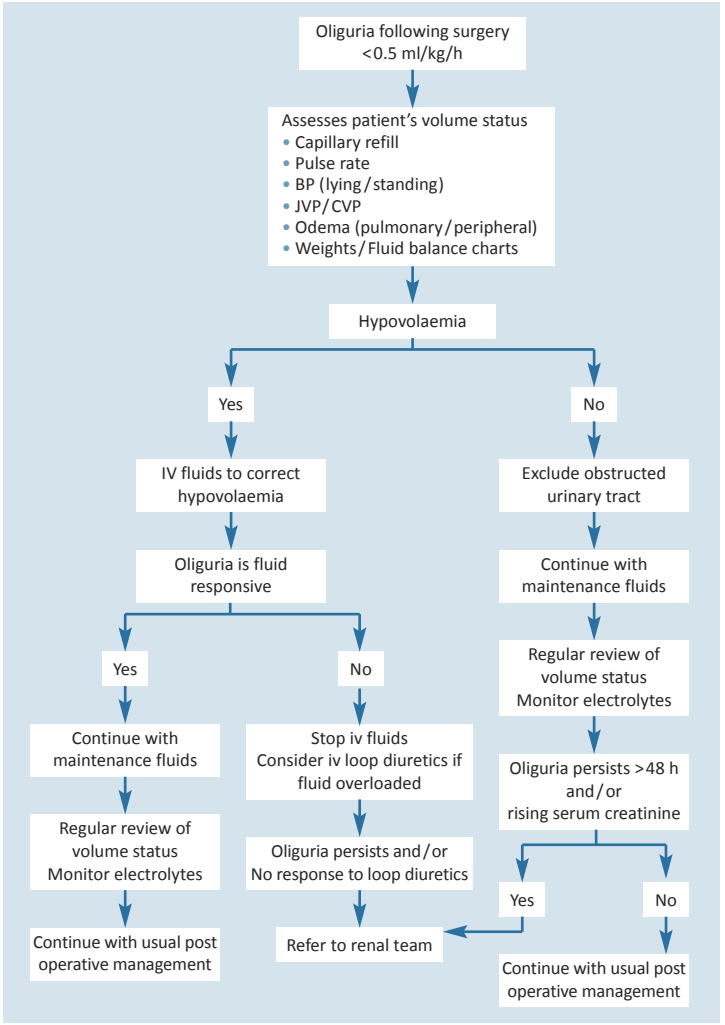


Fig. 9.1: Flow chart for the management of the oliguric surgical patient.

Oliguric AKI secondary to hypovolaemia is either volume responsive or unresponsive. In patients who are fluid responsive, further fluid replacement can be prescribed as hourly fluid input equal to the previous hour's output plus 30 ml, with continuous monitoring and frequent review. In some cases, despite apparently adequate intravascular volume replacement the patient remains oliguric and unresponsive to any further fluid challenge. At this point it is important to avoid precipitating pulmonary oedema and no further intravenous fluid should be administered. If the patient remains hypotensive, treatment with vasopressors should be considered and the advice of the critical care team sought. If the patient is haemodynamically stable but the AKI continues to progress, refer to the renal team.

In addition to the risk of pulmonary oedema, excessive fluid administration has been associated with a worse outcome. A number of studies in surgical patients have demonstrated that a fluid regimen that causes less than 2 kg weight gain, reduces the number of postoperative complications including anastomotic leak, sepsis, and bleeding requiring transfusion[9,57,65]. On the other hand, a positive fluid balance greater than 2.5 kg is associated with increased morbidity[9,57,65].

DIURETICS

A common clinical question with oliguric AKI is whether the administration of loop diuretics (frusemide, bumetanide) improves renal recovery by increasing urine output. Studies have demonstrated that the use of high-dose loop diuretics to increase urine output in patients with established AKI does not decrease the need for renal replacement therapy or improve survival[80-82]. However, they may have a short-term role in managing fluid overload and pulmonary oedema. In these patients, they may be used cautiously to try and establish a diuresis and treat the pulmonary oedema. If the patient fails to respond, referral to the renal team is recommended. It must be remembered that high doses of loop diuretics are not without side-effects and may cause permanent hearing loss.

Chapter 10: ACUTE KIDNEY INJURY

INTRODUCTION

It is important to recognise AKI as a syndrome with many different causes. Failure to identify the cause may lead to misdiagnosis and a missed opportunity to initiate the most appropriate management plan. In many cases the patient will be hypovolaemic in the clinical setting of sepsis and there is, therefore, a need for careful assessment of volume status and the prescribing of intravenous fluids. Adequate initial fluid resuscitation needs to be balanced subsequently with appropriate de-escalation of fluid administration, particularly in patients with volume unresponsive oliguric AKI.

DEFINITION

AKI is a result of a rapid fall in glomerular filtration rate occurring over hours or days. The consequences include a failure to regulate fluid and electrolyte balance and a failure to excrete metabolic waste products and drugs[38,83].

AKI is diagnosed according to the kidney disease improving global outcomes (KDIGO) recommendations when one of the following criteria is met:

- Serum creatinine rises by ≥26 µmol/L within 48 hours or
- Serum creatinine rises ≥1.5 fold from a baseline value measured within the previous week or
- Urine output is <0.5 ml/kg/h for >6 consecutive hours

If serum creatinine concentration has not been measured in the previous week, use the most recent creatinine concentration measured within the last three months. AKI can be staged according to the criteria in **Table 10.1**.

Table 10.1: Stages of acute kidney injury.

Stage	Serum creatinine (SCr) criteria	Urine output criteria
1	increase ≥26 µmol/L within 48 h or increase ≥1.5-1.9 × baseline SCr	<0.5 ml/kg/h for >6 consecutive h
2	increase ≥2-2.9 × baseline SCr	<0.5 ml/kg/h for >12 h
3	increase ≥3 × baseline SCr or increase ≥354 µmol/L or Commenced on renal replacement therapy (RRT) irrespective of stage	<0.3 ml/kg/h for >24 h or anuria for 12 h

Any patient who meets the criteria for AKI should have a thorough clinical evaluation, which includes an assessment of volume status, fluid balance and medication to identify any potential causes for the AKI. In the majority of cases, AKI may be reversible if the cause is identified and appropriate management implemented early enough.

In their laboratory reports the majority of biochemistry departments in England issue an AKI warning to primary and secondary care clinicians, based on rises in serum creatinine (**Fig. 10.1**). Some UK National Health Service (NHS) Trusts have developed AKI care bundles that are linked to AKI warning, prompting the clinician to review the patient and confirm a clinical diagnosis of AKI[84].

Urea & Electrolytes

Result	Value	Units	Reference range
Sodium	**120**	mmol/L	133-146
Potassium	4.5	mmol/L	3.5-5.3
Urea	**21.4**	mmol/L	2.5-7.8
Creatinine	**437**	µmol/L	64-104
eGFR	12	ml/min/1.73m^2	
AKI Warning Stage	**3**		0-0

Figure 10.1: An example of U&E result with an elevated creatinine and AKI warning indicating the patient has AKI Stage 3.

EPIDEMIOLOGY

AKI was previously ill-defined, with multiple definitions making it difficult to describe its epidemiology accurately. The new Kidney Disease Improving Global Outcomes (KDIGO) definition of AKI has provided an opportunity to start to capture data about the incidence of AKI across the world[38,83]. However, it is important to remember that the incidence of AKI will depend upon the available resources to measure serum creatinine in different healthcare systems. In high-income countries there is now an increasing amount of data on the incidence of AKI, based on serum creatinine measurements. Urine output is poorly measured within most healthcare systems and, therefore, reliable data on the incidence of AKI based on urine output are lacking. Analysis of large databases has estimated that 8-16% of all hospital admissions are associated with an episode of AKI[85]. A further consideration is whether the AKI develops initially in the community (c-AKI) or occurs 24 hours after admission to hospital which is regarded as hospital acquired AKI (h-AKI).

AETIOLOGY OF ACUTE KIDNEY INJURY

If the criteria for diagnosing AKI have been satisfied, it is important to identify the underlying aetiology as this will determine the most appropriate therapy and influence whether early referral to the renal team is necessary. AKI can be considered as pre-renal, intrinsic and post-renal (**Fig. 10.2**). Pre-renal and post-renal AKI can both be considered as functional processes that may progress to structural injury to the parenchyma if not treated promptly.

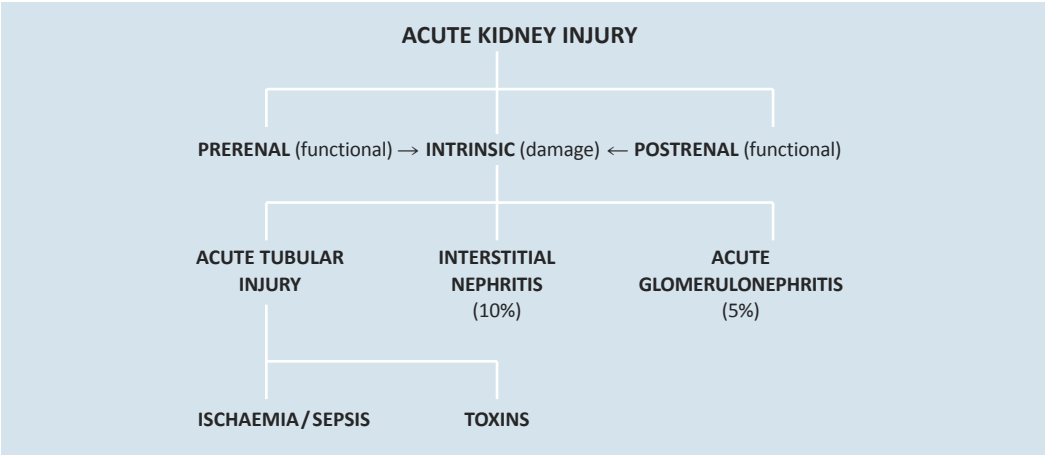


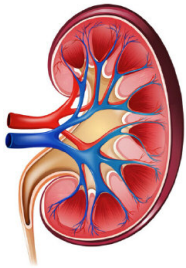
Fig. 10.2: Classification of acute kidney injury.

The most common causes of AKI are:

- sepsis (50%)
- toxins (e.g. gentamicin, NSAIDs)
- hypovolaemia (e.g. blood loss, burns, vomiting and diarrhoea)
- hypotension (e.g. sepsis and continuation of diuretics/antihypertensive drugs)

The aetiology of AKI is commonly multifactorial and secondary to more than one of the above examples. Rarer causes (e.g. vasculitis, interstitial nephritis) must also be considered if the aetiology is not immediately apparent (**Fig. 10.3**). AKI is most commonly secondary to a combination of sepsis and hypovolaemia, resulting in hypoperfusion of the kidneys and initially pre-renal AKI. Failure to correct the hypoperfusion early may result in the development of acute tubular injury and intrinsic AKI, classically referred to as acute tubular necrosis (ATN).

Pre-renal AKI
- Sepsis
- Toxins – IV contrast
- Hypotension
  - Vomiting
  - Diarrhoea
  - Diuretics
  - Haemorrhage
  - Burns
  - Medication
    - ACE inhibitors
  - Cardiac failure
- Hepatorenal syndrome
- Renal artery stenosis



Post-renal AKI
- Kidney stones
- Prostatic hypertrophy
- Tumours
- Retroperitoneal fibrosis

Intrinsic AKI
- Acute tubular injury
- Nephrotoxins
  - Gentamicin
  - IV contrast
  - NSAIDs
  - Rhabdomyolysis
  - Haemoglobinuria
- Tubulointerstitial injury
- Glomerulonephritis
- Myeloma
- Lupus nephritis
- Vasculitis
  - ANCA
- Haemolytic uraemic syndrome
- Thrombotic thrombocytopaenic purpura

Fig. 10.3: Classification and causes of acute kidney injury (adapted from http://www.lhp.leedsth.nhs.uk/detail.aspx?id=3166). ANCA = antineutrophil cytoplasmic antibody.

RISK FACTORS FOR AKI

There are a number of risk factors for AKI, which may either be inherent to the patient or due to exposure to other causes (**Tables 10.2** and **10.3**).

Table 10.2: Inherent risk factors for acute kidney injury.

Inherent risk factors
• Age >75yrs
• Chronic kidney disease (eGFR <60 ml/min/1.73m^2)
• Previous AKI
• Cardiac failure
• Peripheral vascular disease
• Hypertension
• Liver disease
• Diabetes mellitus

Table 10.3: Exposure risk factors for acute kidney injury.

Exposure risk factors
• Sepsis
• Toxins (e.g. gentamicin, NSAIDs, iodinated contrast, poisons)
• Hypovolaemia/hypotension

CLINICAL FEATURES OF ACUTE KIDNEY INJURY

There should be a high index of suspicion for AKI, particularly in an acutely ill patient with known risk factors. Information about the patient's previous kidney function (e.g. serum creatinine), particularly over the preceding 3 months, is a vital part of the evaluation. As in every other clinical condition, diagnosis is achieved by weighing all the evidence derived from a full history, examination and appropriate investigations[86]. Serial changes in clinical parameters are often more revealing than single measurements taken at any one time. AKI should be considered as part of the differential diagnosis in patients presenting with the clinical features described in **Table 10.4**.

Table 10.4: Clinical features of patients with suspected acute kidney injury and recommended baseline investigations.

History	Examination	Investigations

• risk factors
• symptoms predisposing to hypovolaemia
  • vomiting
  • diarrhoea
  • poor oral fluid intake
  • blood/plasma loss
• symptoms suspicious of vasculitis
  • uveitis
  • skin rash or purpura
  • joint pains
  • haemoptysis
• urinary symptoms
  • anuria
  • frequent dribbling or passage of small volumes of urine
  • suprapubic discomfort
• full medication history including
  • over-the-counter medications
  • herbal remedies
	• general
	  • weight
	  • temperature
	  • skin turgor (over clavicle)
	  • mucous membranes (misleading if mouth breathing)
	  • skin rash or purpura (vasculitis)
	  • joint swelling (vasculitis)
	  • uveitis (vasculitis)
	• volume status
	  • capillary refill
	  • pulse rate
	  • jugular venous pressure
	  • BP (lying and standing)
	  • heart sounds (gallop rhythm)
	  • lungs (pulmonary oedema)
	  • peripheral oedema
	• abdomen
	  • bladder distension
	  • intra-abdominal hypertension
	  • rectal or pelvic examination if obstruction suspected
		• full blood count (FBC)
		• urea and electrolytes (U&Es), including chloride and bicarbonate
		• acid-base status (from arterial blood gas analysis)
		• liver function tests (LFTs)
		• calcium and phosphate
		• urinalysis (prior to urinary catheter)
		• ultrasound of renal tract within 24 hours if obstruction suspected

AKI can be oliguric (<0.3 ml/kg/h) or non-oliguric. Pre-renal AKI (functional process) is associated with oliguria by virtue of the fact that there is reduced renal perfusion and intact renal tubules which endeavour to preserve salt and water. Patients with pre-renal AKI that evolves to intrinsic AKI (structural injury) or who experience direct tubular toxicity (e.g. from gentamicin or radiological contrast medium) may lose the ability to reabsorb fluid and are not therefore oliguric, maintaining a relatively normal urine output but with impaired concentration of solutes. These patients will require ongoing fluid therapy to maintain an optimal volume status adequate to excrete waste products. However, failure to establish adequate renal perfusion in these polyuric patients, who are evolving from pre-renal to intrinsic AKI, will ultimately result in oliguria. Careful and continued monitoring is, therefore, imperative.

INVESTIGATIONS

Urinalysis

- blood and/or protein suggest glomerular disease if infection is excluded

Blood biochemistry

- elevated urea and creatinine will trigger an assessment of whether AKI is present
- reduced eGFR will trigger an assessment of whether AKI is present, but eGFR is not used to define or stage AKI
- hypercalcaemia – may occur with widespread cancer in bone, multiple myeloma or hyperparathyroidism
- acidaemia – due to a failure to regenerate bicarbonate
- liver function tests – elevation may occur with hepato-renal failure

Haematology

- anaemia – may occur

Immunology

- myeloma screen (immunoglobulins, serum electrophoreseis, urine for Bence Jones protein)
- Anti Neutrophil Cytoplasmic Antibody (ANCA) – is associated with small vessel vasculitides
- Anti Nuclear Antigen (ANA) – is associated with lupus nephritis
- Complement – is associated with lupus nephritis

Imaging

- renal tract ultrasound scan (USS) to rule out obstruction if suspected. If there are no previous blood tests to confirm whether the patient has AKI or CKD, USS can also be used to assess kidney size. If one of the rarer forms of AKI suspected USS-guided kidney biopsy should be considered

Urinary electrolytes

The measurement of urinary electrolytes and osmolality has been proposed to distinguish pre-renal AKI from intrinsic AKI (**Table 10.5**). However, this assumption may be invalid, since if loop diuretics have been administered within the previous 12 hours or there is pre-existing CKD, the measurements of urinary sodium can be misleading in terms of staging the progression of AKI.

Table 10.5: Distinguishing pre-renal from intrinsic acute kidney injury.

Parameter	Pre-renal	Intrinsic
Urine sodium (mmol/L)	<20	>40
Urine osmolarity (mOsm/L)	>500	<350
Urine:plasma urea ratio	>8	<3
Urine:plasma creatinine ratio (index)	>40	<20
Fractional sodium excretion (%)	<1	>2

PREVENTION OF ACUTE KIDNEY INJURY

Any patient admitted to hospital for major surgery or with acute illness[87] who has any of the risk factors for AKI (**Tables 10.2** and **10.3**) should

- have daily
  - clinical volume status assessment
  - assessment of the fluid prescription
  - fluid balance chart monitoring
  - weighing
- avoid nephrotoxic agents [e.g. non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycosides]
- have other drugs (e.g. antihypertensive medications such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers) reviewed especially if they develop hypotension and/or sepsis. These should be withheld if clinically indicated
- have urea, creatinine and electrolytes checked daily until they regain health

Any inpatient with AKI or risk factors for AKI (**Tables 10.2** and **10.3**) who requires an iodinated contrast study should be considered for alternative imaging or a non-iodinated contrast scan. If an iodinated contrast study is required then the following recommendations should be followed

- highlight the risk to the radiologists
- stop nephrotoxic medication
- volume status assessment to determine whether intravenous volume expansion is required with 0.9% saline
- daily fluid balance chart
- daily weights
- urea, creatinine and electrolytes monitored for 3-5 days

MANAGEMENT OF ACUTE KIDNEY INJURY

Once a patient has developed AKI, treatment is initially supportive but ultimately dependent upon the underlying cause[86,88]. Treatment involves the following:

- Identify and treat the underlying cause (not all AKI will be secondary to hypovolaemia and/or sepsis)
- Volume status assessment
  - If hypovolaemic
    - resuscitate with IV fluids
      - stat fluid bolus of 500 ml (250 ml if cardiac failure present) of crystalloid
      - balanced crystalloid preferred unless risk of hyperkalaemia is present, e.g. AKI secondary to rhabdomyolysis, when 0.9% saline preferred
      - if 0.9% saline commenced switch to a balanced crystalloid
    - consider urinary catheter (but risk of infection) to aid with the assessment of volume status
    - assess clinical response to fluid in terms of
      - capillary refill time
      - pulse (reduction in pulse if tachycardic)
      - jugular venous pressure (rise in JVP)

    - blood pressure (rise in BP)
    - pulmonary oedema
    - urine output (increasing if oliguric)
  - if there is no clinical response and no pulmonary oedema administer further 500 ml of crystalloid, reassess clinically and discuss with a senior member of team
  - if there is a clinical response to a fluid bolus, continue with iv fluids and discuss further fluid therapy management plan with a senior member of team
- If the patient develops oliguric AKI (<0.3 ml/kg/24 h) despite adequate volume resuscitation, consider the patient as having volume unresponsive AKI and refer to the renal team. Further attempts at fluid resuscitation may result in pulmonary oedema.
- If the patient has volume unresponsive AKI continue with iv fluid cautiously, matching urine output and monitoring for signs of respiratory distress (rising respiratory rate, pulmonary oedema or falling oxygen saturations).
- Specific treatment of complications of AKI
  - Hyperkalaemia (see also **Chapter 14**) may be associated with
    - muscle weakness, palpitations, paraesthesia
    - ECG changes: loss of P-waves, wide QRS complexes, peaked T waves
  - It must be remembered that unless the cause of the AKI is treated, the measures described above are only temporary. Serum potassium concentrations will need to be monitored closely until recovery of sufficient kidney function to excrete potassium or institution of renal replacement therapy.
  - Immediate treatment is required if
    - K^+ >6.0 mmol/L and ECG changes are present or
    - K^+ >6.5 mmol/L with or without ECG changes
  - Immediate treatment
    - iv 30 ml 10% calcium gluconate over 2-5 minutes (cautiously, as extravasation can cause tissue damage). This stabilises the myocardium rapidly, but has no effect on serum potassium concentration. Further doses may be required until a reduction in plasma potassium concentration is achieved. Onset of action 2-4 minutes. Duration of action 30-60 minutes.
  - Further treatment
    - 10 U fast acting insulin (actrapid) added to 50 ml of 50% dextrose or 125 ml of 20% glucose infused iv over 20 minutes to increase cellular potassium uptake. Blood glucose must be monitored closely. Onset of action 15-30 minutes. Duration of action 4-6 hours.
    - 10-20 mg salbutamol nebuliser to stimulate cellular potassium uptake. Avoid in patients on beta blockers and/or who have a history of cardiac arrhythmias. Onset of action 30 minutes. Duration of action 2-4 hours.
    - Medication review: stop any drugs that contain potassium or interfere with renal excretion of potassium (ACE inhibitors, angiotensin receptor blockers, beta-blockers, potassium sparing diuretics)
    - Review potassium intake including intravenous fluids and enteral or parenteral feeds
  - Acidaemia
    - pH 7.2-7.4 – there is very little evidence to support correction with bicarbonate.
    - pH <7.2 – isotonic sodium bicarbonate 1.4% solution can be used in stable patients not imminently requiring renal replacement therapy. Bicarbonate therapy may worsen intracellular acidosis and

deliver excessive sodium load. In the presence of hypocalcaemia, bicarbonate can cause a further reduction in calcium and provoke convulsions. Bicarbonate should only be used when the serum calcium concentration is known, and near normal and after obtaining senior medical advice. Renal replacement therapy will be required if the patient is hypervolaemic and/or refractory to medical treatment

- Pulmonary oedema
  - sit the patient up and provide supplementary oxygen (up to 60%) via a Venturi face mask. A non-rebreathing mask (15 L/min O_2) may be required if severe pulmonary oedema is present.
  - buccal glyceryl trinitrate 2-5 mg works rapidly and can be repeated as frequently as required. If intolerable headache or hypotension develop, both resolve rapidly after removing the tablet from the mouth.
  - iv glyceryl trinitrate 50 mg in 50 ml 0.9% sodium chloride. Commence at 2 ml/h and titrate up to 20 ml/h maintaining systolic BP >95 mmHg.
  - iv frusemide can be tried if the patient is haemodynamically stable and adequately intravascularly filled. The dose is dependent on the severity of AKI. Frusemide 160 mg (slow infusion over 1 hour) may be required for severe AKI (stage 3) (**Table 10.5**).
  - if the patient is in extremis with or without mechanical ventilation institute renal replacement therapy
- uraemic encephalopathy
  - renal replacement therapy
- uraemic pericarditis
  - renal replacement therapy

MEDICATION MANAGEMENT

In patients with AKI it is important to identify medications that are normally metabolised and/or excreted by the kidneys, and either avoid or make appropriate dose adjustments. Common examples include:

- penicillins
- cephalosporins
- vancomycin
- morphine (metabolites will accumulate)
- fractionated heparin

If the patient is hypotensive there should be a low threshold for withholding antihypertensive therapy, since these drugs only exacerbate renal hypoperfusion. Common examples include:

- angiotensin-converting enzyme inhibitors
- angiotensin receptor blockers
- diuretics

Nephrotoxic medications should be avoided if possible (unless life-saving) and include:

- non-steroidal anti-inflammatory drugs (NSAIDs)
- gentamicin
- amphotericin

AKI CARE BUNDLES

A number of NHS Trusts have developed AKI care bundles, which prompt the clinician to initiate early patient management[89]. One example is the STOP AKI care bundle (**Fig. 10.4**), which focuses on treating sepsis promptly, optimising blood pressure, optimising volume status, avoiding toxins and preventing harm to the patient. It is essential to identify the underlying cause to provide the definitive treatment.

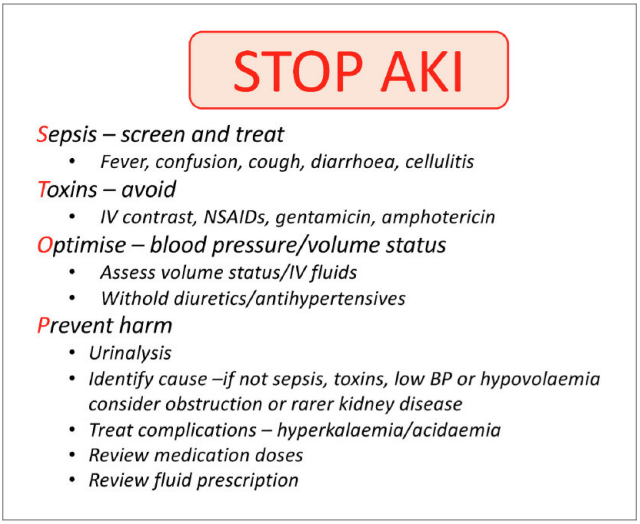


Fig. 10.4: STOP AKI Care Bundle (www.aki.org.uk).

REFERRAL TO RENAL TEAM

- NOT all patients diagnosed with AKI need to be referred
- Prior to referral the following should be performed
  - a thorough clinical history and examination (including fluid balance assessment)
  - initial investigations (as recommended in **Table 10.5**)
  - initial supportive management (as recommended above)
- Early renal referral is recommended in the following patients
  - AKI stage 3 (serum creatinine ≥3 × baseline value) (**Table 10.2**)
  - persistent oliguria and/or rising serum creatinine despite supportive therapy
  - complications refractory to medical treatment
    - hyperkalaemia (serum K^+ >6 mmol/L)
    - pulmonary oedema
    - acidaemia (pH <7.15)
    - uraemic encephalopathy
    - uraemic pericarditis

- suspicion of rarer renal disease
  - absence of defined cause, e.g. sepsis or hypovolaemia
  - systemic features e.g. rash, uveitis, joint pains, blood and protein on urinalysis
  - hypercalcaemia and paraprotein
  - bloody diarrhoea, haemolysis and low platelets
- poisoning suspected
  - ethylene glycol
  - methanol
  - lithium

RECOVERY

The first signs of recovery from oliguric AKI may be an increase in urine output followed by a reduction in the incremental daily rise in serum creatinine followed by a plateau and an ultimate fall in the creatinine concentration.

Recovery from AKI can result in a polyuric state in some patients with the production of large urine volumes until the capacity of the renal tubule to concentrate urine returns. There must, therefore, be continuing careful attention to the patient's volume status and fluid requirements.

During this polyuric recovery phase, patients can be at risk of developing a free water deficit, manifest as hypernatraemia, which requires an increased intake of water (intravenous 5% dextrose if unable to drink). Failure to address the free water deficit promptly will not only slow renal recovery but will also put the patient at risk of the neurological complications of hypernatraemia. Another potential complication is the development of hypokalaemia, which requires appropriate therapy due to the risk of cardiac arrythmias and ileus. A balanced crystalloid containing potassium is recommended in this clinical context. Additional potassium supplementation may also be necessary.

FOLLOW UP

AKI is a recognised antecedent for CKD and patients therefore require follow up.

The discharge summary to primary care should include:

- the cause of AKI
- risk factors for AKI
- medications stopped and when to be re-started
- kidney function on discharge
- longer-term monitoring requirements, e.g. blood pressure, U&Es, urinary protein

Patients with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 should be referred to the renal team for follow-up.

OUTCOMES FROM ACUTE KIDNEY INJURY

AKI is associated with worse patient outcomes[90-92] including increased

- length of stay
- mortality
- risk of chronic kidney disease (CKD)
- cost (£1 billion/year in the UK)

Chapter 11: CHRONIC KIDNEY DISEASE

INTRODUCTION

There are many causes of CKD, which leads to irreversible loss of kidney function over a period of months to years. The incidence of CKD has increased by 89% over the last 3 decades[93] . The predominant reason for this is an increase in the number of cases secondary to diabetes mellitus and glomerulonephritis, with fewer cases due to hypertension.

DEFINITION OF CHRONIC KIDNEY DISEASE

CKD is defined by an eGFR less than 60 ml/min/1.73m^2, by the presence of markers of kidney damage (structural or albuminuria), or both, for at least 3 months. The term CKD now replaces the term chronic renal failure and is categorised into 5 stages using the eGFR expressed as ml/min/1.73 m^2 (**Fig. 11.1**).

The eGFR is an estimate of the GFR and can be calculated simply, using either the MDRD (Modification of Disease in Renal Disease)[54] or the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation[94] based on age, sex and serum creatinine. The CKD-EPI equation has been reported to perform better and with less bias than the MDRD equation, especially in patients with higher GFR. The calculated eGFR needs to be interpreted with caution when tested in different hospitals as the value is dependent upon which equation each laboratory uses.

More information on eGFR and the MDRD and CKD-EPI equation[94] can be found at www.mdrd.com along with an eGFR calculator.

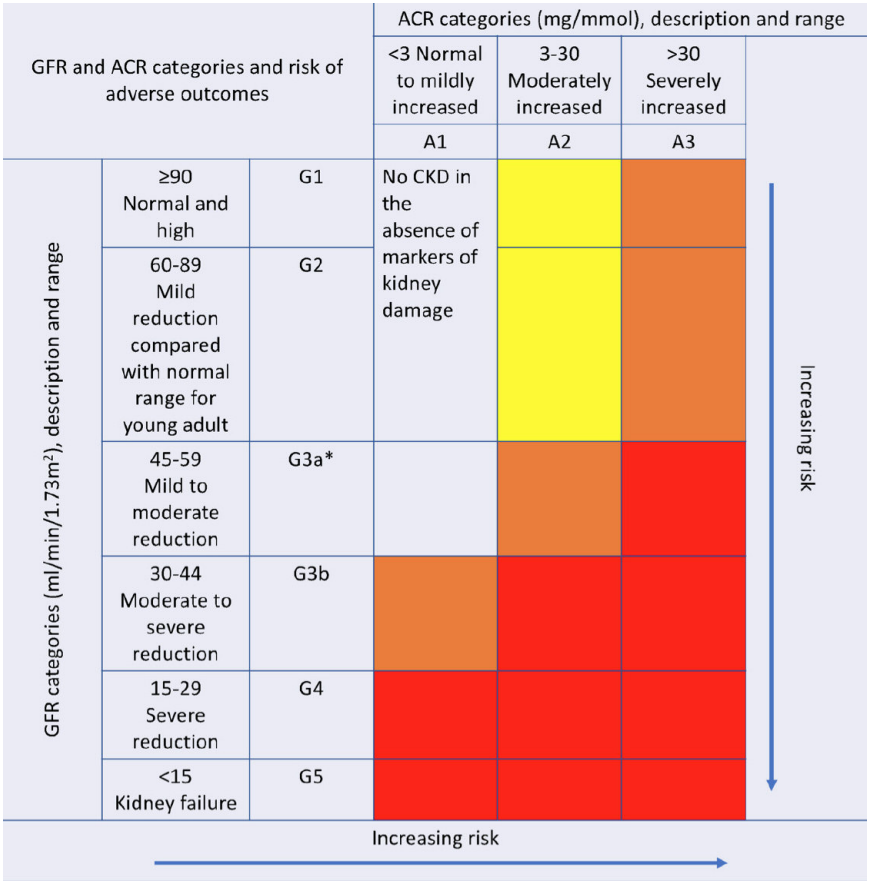


Fig. 11.1: Staging of chronic kidney disease (ACR=albumin:creatinine ratio in the urine) – Modified and redrawn from[38].

By definition, the diagnosis of CKD requires two serum creatinine values measured at least 90 days apart. Previous blood tests are, therefore, necessary to ascertain if someone has CKD.

EPIDEMIOLOGY OF CHRONIC KIDNEY DISEASE

The incidence and prevalence of CKD, which increases with age[95] varies according to ethnicity, social class and country. The prevalence is reported to be about 11% in high-income countries and is rising worldwide, representing a significant burden on healthcare resources.

AETIOLOGY OF CHRONIC KIDNEY DISEASE

There are many causes of CKD, but the most common are diabetes, glomerulonephritis and hypertension. Diabetes accounts for 30-50% of all causes of CKD.

- Disease
  - Diabetes mellitus
  - Hypertension
  - Congenital and inherited disease
    - Autosomal dominant polycystic kidney disease
    - Alport Syndrome
  - Glomerular disease
    - Primary disease, e.g. membranous nephropathy
    - Secondary disease, e.g. lupus nephritis
  - Vascular disease
    - Renovascular disease
  - Tubulo-interstitial disease
    - Infection
    - Drugs, e.g. proton pump inhibitors
  - Acute kidney injury – even patients with recovery of kidney function after AKI are at high risk of CKD[92]
  - Urinary tract obstruction
    - Renal stone disease
    - Prostatic disease
- Environmental Factors
  - Outdoor and agricultural work and lack of shade are associated with a rapid fall in eGFR[96]

CLINICAL FEATURES OF CHRONIC KIDNEY DISEASE

CKD can develop insidiously, without apparent symptoms or signs until an advanced stage (eGFR <15 ml/min/1.73m^2).

The symptoms may include:

- Nausea
- Lethargy
- Shortness of breath (anaemia, acidaemia, pulmonary oedema)
- Insomnia
- Nocturia (decreased ability to concentrate urine)
- Pruritis (uraemia, hyperphosphataemia)
- Paraesthesia
- Restless legs
- Muscle weakness
- Bone pain (metabolic bone disease)
- Ankle oedema (salt and water retention)

The clinical signs may include:

- Pallor (anaemia)
- Excoriation (pruritus)
- Hypertension (salt and water retention)
- Pericardial friction rub (uraemia)
- Pulmonary oedema (salt and water retention)
- Peripheral oedema (salt and water retention)

INVESTIGATIONS

Urinalysis

- blood and/or protein suggest glomerular disease if urine culture is negative (**Fig. 11.2**)

Biochemistry

- elevated urea and creatinine and reduced eGFR
- hyperkalaemia – can occur due to failure to excrete potassium
- acidaemia – can occur due to failure to regenerate bicarbonate
- hypocalcaemia – occurs in advanced CKD due to decreased production of activated Vitamin D
- hyperphosphataemia – occurs in advanced CKD due to decreased urinary excretion

Haematology

- anaemia – occurs in advanced CKD due to decreased secretion of erythropoietin
- platelet dysfunction and easy bruising – effect of uraemia

Immunology

- myeloma screen (immunoglobulins, serum electrophoreseis, urine for Bence Jones protein. Suspect if hypercalcaemia present)

Imaging

- CXR – interstitial fluid with salt and water retention
- renal tract ultrasound scan (USS) to assess kidney size (small scarred kidneys are consistent with CKD)

ECG

- Voltage criteria for left ventricular hypertrophy with long standing hypertension
- Peaked T waves, loss of P waves, widened QRS complex occur in hyperkalaemia

Fig. 11.2: Urinalysis report demonstrating positivity for blood and protein in a patient with CKD secondary to glomerular disease. Note leucocytes and nitrites are negative making a urinary tract infection unlikely.

MANAGEMENT

Management of CKD should aim to slow disease progression and treat metabolic complications[97]. Patients with CKD are more likely to be hypertensive because of their kidney disease, resulting in more rapid progression of the disease. Serum cholesterol concentrations must be closely monitored and treated.

Treatment

- Stop smoking
- Weight loss/increased exercise
- Blood Pressure
  - In CKD aim for <140/90 mmHg
  - In CKD and diabetes and/or albumin:creatinine ratio (ACR) ≥70 mg/mmol aim for <130/80 mmHg
  - Medication
    - Angiotensin converting enzyme inhibitor (ACEi)
      - Ramipril
    - Diuretic
      - Thiazide (not effective if eGFR <15 ml/min/1.73m^2)
    - Calcium channel blocker
      - Amlodipine
- Fluid balance (salt and water retention)
  - No robust evidence that reduced salt intake can prevent CKD or its progression[98]
  - Loop diuretics e.g. frusemide
- Hypercholesterolaemia
  - Statins

Treatment of complications

- Hyperkalaemia
  - reduce dietary intake
  - correct acidaemia
  - potassium binding resins
- Acidaemia
  - sodium bicarbonate tablets
- Metabolic bone disease
  - phosphate binders (these are tablets taken with meals that bind to phosphate from food in the gut and allow it to be excreted and not absorbed)
  - vitamin D analogues
- Anaemia
  - replete iron stores
  - subcutaneous erythropoietin therapy
- Pruritus
  - antihistamines

Specific therapy

Tolvaptan has been demonstrated to slow the decline in eGFR compared with placebo in patients with later stage autosomal dominant polycystic kidney disease[99].

Those patients who develop end stage kidney disease may choose to have renal replacement in the form of dialysis (haemodialysis/peritoneal dialysis) or kidney transplantation. Patients who do not wish to have dialysis are offered conservative care aimed at symptom control.

Intravenous fluid and electrolyte therapy in patients with CKD

Patients with progressive late stage CKD have reduced sodium filtration, suppression of fluid reabsorption, and ultimately volume overload. They are also at higher risk of hypertension, left ventricular hypertrophy, cardiac failure and oedema, and are likely to be on a number of medications including ACE inhibitors and diuretics. Patients with CKD require higher doses of loop diuretics to enable the drug to be transported across the tubule and reach the active site on the ascending limb of Henle. Such patients have less reserve kidney function and are at increased risk of electrolyte complications, e.g. hyponatraemia, and hypo- or hyperkalaemia.

Patients with CKD are also at increased risk of AKI, and those with CKD Stage 4 and 5 on diuretics and ACE inhibitors who develop AKI are at higher risk of hyperkalaemia. If the cause of AKI is hypovolaemia and hypotension, then these drugs (diuretics and ACE inhibitors) need to be withheld. Clinical signs need to be interpreted carefully in patients with previous advanced CKD who develop AKI as they may have pre-existing peripheral oedema even in the presence of acute hypovolaemia.

Intravenous fluid resuscitation should be carefully monitored, recognising that baseline kidney function will not be normal. Excessive fluid resuscitation and failure to de-escalate the fluids appropriately will result in volume overload. Potassium containing fluids should be used with caution as the patient may already have an excess potassium load and be at a higher risk of hyperkalaemia.

OUTCOMES

The majority of patients with CKD do not progress to advanced stages of CKD because they die earlier from cardiovascular disease. However, the burden of CKD is substantial and, according to the WHO global health estimates, is responsible for 1.5% of deaths worldwide, being ranked 14th in the list of leading causes of death at 12.2 deaths per 100,000 people, a rate which is predicted to rise to 14 deaths per 100,000 people by 2030. A retrospective cohort study of patients with severe CKD demonstrated that, over a five-year period of follow up, 53% of patients died, with 24% having had a cardiovascular event[100].

Chapter 12: FLUID OVERLOAD AND THE DE-ESCALATION PHASE

INTRODUCTION

Acutely ill patients requiring fluid resuscitation to restore haemodynamic stability invariably develop some degree of positive salt and water balance causing tissue oedema. Such overload may be a necessary price to pay for adequate resuscitation and survival. This is a particular problem in patients who go on to develop oliguric AKI as the kidneys are unable to excrete the excess salt and water load until recovery of renal function.

Often the patient has sepsis or an inflammatory state which causes increased vascular permeability and leakage of fluid into the interstitial space. This necessitates the administration of even more fluid to maintain the intravascular volume, cardiac output and tissue oxygen delivery[20] (see **Chapter 1**). It has been shown, for example, that during the first 48 hours of resuscitation of a patient with sepsis, total body water may increase by up to 12.5 L, an excess which may take up to 3 weeks to excrete[101]. It is, therefore, important to recognise when patients have been resuscitated adequately, and their condition has been optimised and stabilised (**Fig. 12.1**). At this stage, fluid intake should be reduced to that which meets maintenance or replacement requirements (see **Chapter 7**). Failure to de-escalate fluid therapy at this stage may result in continued and unnecessary positive salt and water balance.

All patients receiving resuscitation fluids should be monitored with fluid balance charts, regular clinical assessment for signs of volume overload and, if possible, by regular weighing. Healthcare professionals should be alert to any early signs indicating the development of oliguric AKI and should recognise when this has become unresponsive to fluid administration – the point when the patient has been adequately resuscitated but remains oliguric[88]. If haemodynamic stability has been achieved, fluid administration should be curtailed to reduce the risk of pulmonary oedema, a common iatrogenic consequence of overzealous fluid resuscitation. On the other hand, if the patient remains haemodynamically unstable, the use of vasopressors should be considered rather than continuing fluid resuscitation.

DE-ESCALATION PHASE

The period of clearance of excess salt and water acquired during resuscitation, optimisation and stabilisation is described as the de-escalation phase[102,103] **(Fig. 12.1**).

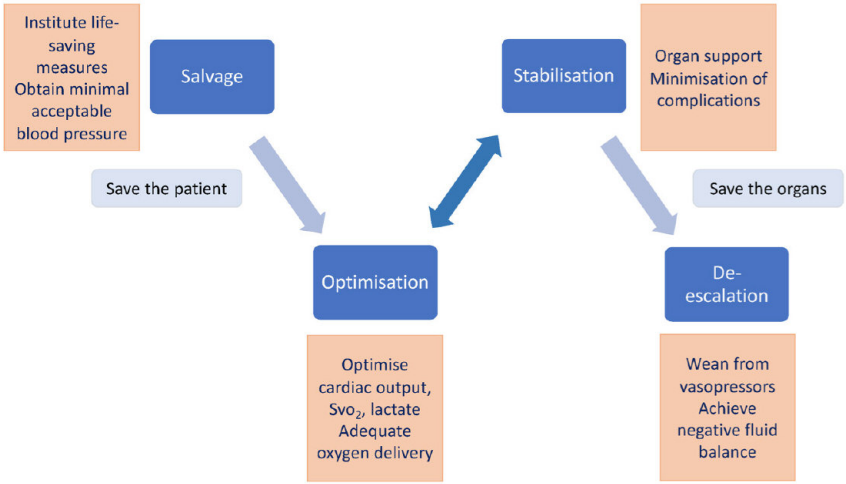


Fig. 12.1: The four phases in the treatment of shock. The patient may progress through all four phases in a continuous manner. However, some patients may oscillate between the optimisation and stabilisation phases before finally progressing to the de-escalation phase (Modified and redrawn from Vincent and De Backer[102] and Hoste et al.[103]).

During the de-escalation phase the aim should be to prevent further unnecessary salt and water overload and to promote excretion of the accumulated excess, with the aim, as far as possible, of restoring organ function and normal fluid balance. Oral intake should be started as soon as possible. It is only too easy to overload patients with intravenous salt and water, whereas it is difficult to do so by the oral route. Salt and water intake, by whatever route, should be limited to that which meets maintenance requirements and replaces any additional losses, e.g. from intestinal fistulae or gastric aspiration. One of the major causes of unnecessary fluid overload is a failure to make a timely adjustment of the fluid prescription from resuscitation to maintenance mode. During the de-escalation phase, prescription of fluids should allow a small negative balance each day, as the patient's ability to excrete a salt and water load returns (the sodium and water diuresis phase of injury[18]). The rate at which this transition can be achieved may vary from patient to patient according to the natural history and severity of their particular illness. This process requires careful monitoring to strike a balance between getting rid of the interstitial fluid overload and avoiding depletion of intravascular volume[104].

The natural excretion of salt and water by the kidneys is dependent on underlying kidney function and the stage of recovery from acute illness. Persistent sepsis and/or hypovolaemia delays the recovery from AKI and the ability to excrete salt and water.

THERAPEUTIC OPTIONS IN THE DE-ESCALATION PHASE

The therapeutic options, apart from allowing a gradual drift into negative fluid balance, as described above, include the use of loop diuretics or ultrafiltration using renal replacement therapy.

Prior to deciding on the most appropriate therapeutic approach to a particular patient, a full clinical evaluation of volume status including an assessment of fluid balance is necessary. Loop diuretics, it must be remembered, act on the ascending limb of Henle to prevent the reabsorption of sodium, potassium, chloride and water. It, therefore, means that there must be sufficient renal blood flow and perfusion for the diuretics to be delivered to their point of action. In the presence of intravascular hypovolaemia, the kidneys are relatively unresponsive to diuretics which are, therefore, inappropriate and possibly harmful under these conditions. It is recommended that diuretics should only be used in patients who are both adequately intravascularly filled and haemodynamically stable. The assessment of the response requires daily clinical examination of volume status with review of the urea and electrolytes, urine output and daily weighing. There is no evidence to support the use of diuretics to treat AKI *per se* and this should not be encouraged. However, in the presence of both severe fluid overload and AKI, a trial of diuretics may be warranted[105,106]. Patients who fail to recover kidney function and yet remain severely volume overloaded despite the use of diuretics will need referral to the renal team for a further evaluation of the cause of the AKI and consideration of renal replacement therapy (RRT) to remove excess fluid and electrolytes[107]. Treatment with diuretics also runs the risk of hypernatraemia with a true water deficit, and a failure to recover kidney function. There must, therefore, be careful daily review of the patient's fluid and electrolyte status to assess the response to the continued administration of diuretics.

CRITICALLY ILL PATIENTS

Volume overload in the critically ill patient can be difficult to quantify precisely and has been strongly associated with adverse outcomes. Critically ill patients who have received large volumes of fluid in the resuscitation phase may still require vasopressor support. In those requiring RRT, usually for the correction of acid-base and electrolyte abnormalities secondary to AKI, there is an opportunity, as the haemodynamic status improves, to increase the volume of fluid removal by RRT[107]. Care must be taken to do this without causing intravascular hypovolaemia and a relapse into haemodynamic instability[108].

Chapter 13: THE PATIENT WITH DIABETES MELLITUS

INTRODUCTION

With better management of diabetes mellitus in recent years, admissions due to loss of control with or without ketosis are less frequent than in former times. Nonetheless, cases of decompensated diabetes with keto-acidosis (DKA) or hyperosmolar non-ketotic (HONK) syndrome form an important part of every doctor's experience of acute medicine[109-112]. Similarly, with the rising prevalence of diabetes, particularly type 2, the perioperative fluid and metabolic management of diabetic patients has become increasingly important[113-115].

DECOMPENSATED DIABETES

Type 1 diabetes[109,110]: insulin secretion is impaired in most cases by >90%. This means that, with reduced or absent administration of insulin or with increased insulin demand due to intercurrent illness, not only does the blood glucose rise but control over fat and protein metabolism is lost, leading to keto-acidosis (β-hydroxybutyrate being the main keto-acid) and protein catabolism.

Type 2 diabetes[111,112]: This is associated initially with insulin resistance but only partial loss of secretion. At this stage, there is usually sufficient circulating insulin to prevent ketosis but not to control the blood glucose. Decompensation usually presents with HONK in which the blood glucose rises to higher levels than those seen in DKA (it only takes a fraction of the amount of insulin to control ketosis than it does to control blood glucose). With loss of insulin secretion over the years and with severe intercurrent illness, patients with type 2 diabetes can develop ketoacidosis, requiring insulin, even though they may be able to revert to tablet treatment afterwards.

DKA[109,110] and **HONK**[111] represent the two extremes of the spectrum of decompensated diabetes (**Table 13.1**), although intermediate cases are not infrequent, depending on the precipitating cause and the percentage loss of insulin secretion. In both situations, hyperglycaemia causes an osmotic diuresis with excessive urinary losses of salt, water, and potassium, leading to ECF and intravascular volume depletion and the risk of AKI.

With both types of decompensation, potassium is lost from cells due to catabolism of glycogen and protein. It is then excreted in the urine causing a deficit, which only becomes apparent as hypokalaemia once the anabolic effect of insulin treatment is felt. In severe cases the rate of K^+ loss from cells, combined with AKI, can cause hyperkalaemia (>5.5 mmol/L) with the risk of cardiac arrest.

The presence of acidosis may present diagnostic problems. Although most patients with ketonuria and features of metabolic acidosis are suffering from ketoacidosis, this cannot always be assumed, particularly where there are other potential causes of acidosis, e.g. renal or circulatory failure. If large volumes of 0.9% saline have been used for resuscitation, a hyperchloraemic acidosis may be imposed on the underlying metabolic changes. For these reasons and to establish the diagnosis beyond doubt it is important to measure blood concentrations of lactate, chloride, and ketones. Arterial blood gas analysis should also be performed and the anion gap or the strong ion difference should be calculated.

Table 13.1: Features of DKA and HONK compared (approximate values only).

Parameters	Normal range		DKA		HONK
		Mild	Moderate	Severe	
Blood glucose mmol/L	3.5-11.1 (random)	>14	>14	>14	>30
Arterial pH	7.35-7.45	7.2-7.3	7.0-7.2	<7.0	>7.3
HCO_3^- mmol/L	22-30	15-18	10-15	<10	Normal to slightly reduced
Urine ketones	Absent	++++	++++	++++	±
Anion gap (mmol/L)	5-10	>10	>12	>12	Variable
Serum osmolality mOsm/kg	280-295	280-320	280-320	280-320	>320
Average total losses					
Water (litres)		3-4	4-5	>5	6-10
Sodium (mmol)		200-280	280-350	>350	350-700
Potassium (mmol)		200-280	280-350	>350	>350

Treatment

The aims of treatment are similar in both DKA and HONK, although with differences of emphasis.

- Restore the circulation and the ECF deficit by initially rapid fluid infusion. This also has a beneficial metabolic effect by reducing the blood glucose, addressing circulatory failure and AKI, and reducing both acidosis and serum potassium concentration.
- Seek the underlying cause of the diabetic decompensation (e.g. sepsis) and treat it.

Fluids and insulin

- In the absence of shock or oliguria, give 1-2 litres of crystalloid (see below) in the first 2 hours, then 1 litre over the next 4 hours and 4 litres over the next 24 hours. In severe cases, administration should be faster initially, aiming to correct half the fluid deficit within the first 6 hours and the remainder over the ensuing 24 hours. With HONK the fluid deficits are larger (**Table 13.1**)
- After the first litre of fluid add KCl 20-40 mmol to each subsequent litre of fluid infused, depending on the changes in serum K^+ with treatment.
- To avoid precipitating cerebral oedema, the effective serum osmolality should not be reduced at a rate greater than 3 mOsm/kg/h. This is particularly important in cases involving children or the elderly and in the treatment of HONK.
- When the blood glucose has fallen to 14 mmol/L, change to a hypotonic (e.g. 0.45% saline in 5% dextrose) glucose-containing solution adjusted according to the insulin-induced changes in blood glucose and the serum sodium and osmolality.
- Treat acidosis with fluid infusion, insulin, and, in severe cases (pH <7.0), with bicarbonate

- If serum potassium concentration exceeds 5.5 mmol/L, this will usually respond to infusion of fluid and insulin. However, in patients with AKI or higher potassium concentrations, adopt the regimen recommended in **Chapter 10**.
- Reduce blood glucose and ketones with insulin infusion. It may take up to 48 hours to clear ketones if DKA is severe. Add 50 U soluble short-acting insulin to 50 ml 0.9% saline in a syringe driver and administer intravenously at 6 U/h, adjusting subsequently to lower the blood glucose at a rate no faster than 4 mmol/L/h.

Monitoring

- Monitor blood glucose, urinary ketones, acid-base status, serum potassium, sodium, chloride and, if appropriate, osmolality, every hour or two initially. Watch particularly for a fall in serum potassium and correct this with increased potassium input to maintain serum K^+ in the range of 3.3-4.5 mmol/L. Monitor clinical status, vital signs, kidney function and urine output.

Fluid Prescription

Traditionally, 0.9% saline has been used for resuscitation, followed by 0.45% saline in 5% dextrose and KCl as the volume deficit nears restoration. Recent studies suggest that using a balanced electrolyte solution avoids the hyperchloraemic acidosis associated with administration of 0.9% saline although there is currently no evidence concerning its clinical advantage in this situation.

Hypotonic solutions pose a risk of too rapid a fall in osmolality unless the plasma sodium and osmolality are monitored carefully and the infusion rate controlled accordingly. It should be remembered that glucose acts like Na^+ as an ECF osmotic agent, so that as the blood glucose falls with insulin treatment, water passes from the ECF to the ICF, thereby raising the ECF sodium concentration by 1.6 mmol/L for every 5.6 mmol/L fall in blood glucose. It is common, therefore, particularly in HONK, to see the plasma Na^+ rise with treatment, necessitating a switch to a more hypotonic solution. It is at this point that switching from 0.9% to 0.45% saline may be useful gradually to reduce the plasma Na^+ to normal.

Although there is a phosphate deficit in decompensated diabetes, and phosphate concentration falls with treatment, phosphate supplementation has not been shown to be beneficial.

SURGERY IN THE PATIENT WITH DIABETES

This section gives only a very brief outline of the subject. For more complete advice, the reader is urged to consult recently published guidelines[113-115].

Perioperative glucose control

For short procedures, involving missing no more than one meal, particularly in patients with Type 2 diabetes, the normal treatment may be delayed until postoperatively, with hourly monitoring of blood glucose and treatment of diabetes with insulin if blood glucose rises above 12.0 mmol/L.

Those expected to miss more than 1 meal, particularly patients with Type 1 diabetes should receive variable rate insulin infusion (VRII) to maintain blood glucose within the range 4-12 mmol/L as shown by hourly monitoring. Insulin should be administered in 0.45% saline in 5% glucose and KCl 20-40 mmol/L (depending on the presence of hypokalaemia) via a syringe pump, starting approximately 6 hours preoperatively and continuing postoperatively until normal oral intake is established.

Perioperative fluid and electrolyte management

The principles are the same as those we have outlined for the patient without diabetes. In the patient with Type 1 diabetes, however, in order to avoid ketosis, it is useful to have a constant rate of infusion of a crystalloid containing 5% glucose with appropriate VRII cover. This can be achieved using 0.45% saline with 5% dextrose and 20 or even 40 mmol KCl/L, depending on the serum potassium concentration. Alternatively, if a multi electrolyte-containing solution is preferred, use Plasma-Lyte 56 Maintenance if available (see **Chapter 6**).

Chapter 14: DISORDERS OF SODIUM, POTASSIUM, CALCIUM, MAGNESIUM AND PHOSPHATE

INTRODUCTION

It is impossible to give a detailed account of all aspects of these electrolytes in a brief chapter such as this. We have, therefore, confined ourselves to a short summary of some common aspects. For more detailed treatment of the subject the reader is referred to excellent review articles and books[10,55,116-119].

SODIUM (Na^+)[119]

The total body sodium is 3000-4000 mmol (69-92 g), of which only 60% is exchangeable, the remainder being locked mainly in bone. The required daily intake in health to maintain balance is about 1 mmol/kg body weight. Short-term changes in the serum sodium concentration are usually due to changes in water balance, although, in some cases, changes in salt balance may contribute. This reflects the fact that salt balance relates mainly to maintenance of volume, whereas water balance is more concerned with osmolality. Hyponatraemia and hypernatraemia, resulting from excess or deficit of water, may occur in the presence of positive, negative or zero salt balance. The serum sodium concentration on its own, therefore, cannot be used to diagnose the state of sodium balance, although if change in water balance is known from serial weighing, then the day-to-day balance of sodium can be inferred from the change in serum sodium concentration over the same period (see **Chapter 5**).

Hyponatraemia

In severe cases with serum sodium <120 mmol/L, there is a risk of developing cerebral oedema and brain damage, particularly in children and the elderly. Conversely, too rapid correction of severe hyponatraemia may also cause neurological damage (osmotic demyelination). It is advised that hyponatraemia be corrected at a rate not exceeding 8-10 mmol/L/day.

In the differential diagnosis of hyponatraemia, pseudo-hyponatraemia should be excluded. Milky serum due to severe hyperlipidaemia, may cause the serum sodium concentration to be falsely low since the lipid expands ECF volume but contains no sodium.

Similarly, hyperglycaemia expands ECF volume by its osmotic action and, as the blood glucose falls with treatment of decompensated diabetes (see **Chapter 13**), water passes from the ECF to the ICF and the sodium concentration rises. Conversely, serum sodium concentration falls by 1.6 mmol/L for every 5.6 mmol/L rise in plasma glucose. In cases of hyperglycaemia, therefore, the serum sodium concentration should be corrected upwards appropriately. It is the corrected value that should guide fluid replacement.

Some clinical causes of hyponatraemia are listed below:

- Positive water and salt balance: This often occurs as a result of infusions of hypotonic fluid postoperatively, following trauma, or during acute illness, when the metabolic response to injury prevents excretion of any salt and/or water excess and impairs the ability of the kidney to correct a low serum osmolality by increasing free water clearance (see **Chapter 1**). In this situation there is usually a positive sodium balance, but a proportionally greater positive water balance. Urinary sodium concentrations are usually low since, during the salt and water retention phase of injury, the normal physiological relationship between sodium balance and urinary sodium is lost. Treatment consists mainly of stopping or reducing intravenous fluids until normal fluid balance is regained.

- Positive water and normal or slightly negative salt balance. This occurs with the syndrome of inappropriate ADH secretion (SIADH), classically associated with small cell carcinoma of the lung, but is also caused by a number of other conditions. With water retention in SIADH, the serum sodium is diluted, but the urinary sodium is normal or high, as the kidneys respond to the slight hypervolaemia and the associated reduction in aldosterone secretion. This condition is often over-diagnosed and should not be confused with the far more common response to injury described above in which the urinary sodium is usually low. SIADH can be treated with water restriction, supplemented in some cases with thiazide diuretics.

- Normal water balance and negative salt balance. This classically occurs in Addison's disease with its loss of both mineralocorticoid and glucocorticoid secretion and clinical features of weakness, weight loss, pigmentation and hypotension. Hyponatraemia occurs not only due to renal salt loss, but also due to the impaired ability of the kidney to correct osmolality; firstly because salt loss causes ECF hypovolaemia, which stimulates ADH secretion, and secondly because glucocorticoids have a permissive role in the distal tubule, allowing urinary dilution. In their absence, free water clearance is impaired, the basis for the old Kepler water load test for the condition. Nowadays diagnosis is made simply by measuring serum cortisol concentrations and their response to Synacthen (the short Synacthen test).

- Water excess and negative sodium balance. This occurs when salt losses from the gastrointestinal tract or the kidneys (diuretics or tubular disease) are combined with excess water or hypotonic fluid intake by mouth or other routes. The sodium depletion causes hypovolaemia, which, in turn, stimulates not only the renin angiotensin aldosterone system (RAAS) but also ADH secretion, thereby impairing free water clearance and any osmolar correction.

- Diuretics. Diuretics may cause problems, especially among older adults, in whom hyponatraemia is not uncommon. The taking of regular thiazide or loop diuretics in a fixed dose may result in negative sodium and potassium balance, particularly during periods of reduced intake due to intercurrent illness. Combined with normal or elevated water intake, this results in both hyponatraemia and sodium deficit. These cause mental confusion and, due to a diminished ECF, fainting and falls. To prevent this problem, it has been our practice to teach patients to adjust their diuretic dose according to daily weight (reflecting fluid balance). If weight is unchanged or lost during the previous 24 hours the dose is omitted. Conversely a gain in weight warrants a normal or increased dose. Patients soon learn to titrate their own diuretic dose in this way.

- Sick cell syndrome. In severe catabolic illness e.g. burns[120], septicaemia, etc., cell membrane function may be impaired and the sodium pump affected so that intracellular sodium concentrations rise and those in the ECF fall despite considerable positive sodium balance[3]. This has been called the 'sick cell syndrome'. With improved tissue perfusion and oxygenation and correction of underlying sepsis this may resolve. In the past, insulin, glucose and potassium have also been used with effect. With improved care of patients with severe injury and critical illness, the sick cell syndrome has become less common.
- Hypernatraemia. The most common cause is net loss of hypotonic fluid from the gastrointestinal tract, e.g. from vomiting and diarrhoea so that, in relation to plasma, proportionately more water is lost than sodium, even though sodium balance is also negative. A similar effect occurs with renal losses due to the osmotic diuresis associated with uncontrolled diabetes. Large fluid losses from sweat (hypotonic fluid with a sodium concentration of around 50 mmol/L), e.g. in the tropics, cause similar changes. The rare primary hyperaldosteronism also causes mild hypernatraemia. Treatment is with hypotonic fluids orally, enterally or intravenously with frequent monitoring of serum biochemistry. Oral water may be sufficient in mild cases. In the presence of diarrhoea, oral rehydration solutions may be appropriate. Severe cases should be treated cautiously with hypotonic intravenous fluids (e.g. 5% dextrose, 0.18% saline in 4% dextrose) taking care to avoid too rapid reduction in plasma sodium or osmolality, which can precipitate cerebral oedema. Correction should be achieved slowly over 48 hours, at a rate no greater than 2 mmol/L/h.

CHLORIDE (Cl^-)[55]

Chloride is the main anion of the ECF at a concentration of 95-105 mmol/L. Unfortunately, because most clinical chemistry laboratories do not report the serum chloride concentration as part of routine biochemical screening, abnormal states such as hyperchloraemic acidosis have sometimes gone undetected. As a consequence, metabolic acidosis due to chloride excess has not infrequently been mistaken for other causes of acidosis, leading to inappropriate treatment. We, therefore, advise that serum chloride should always be measured in the presence of a metabolic acidosis or whenever large volumes of saline have been administered. It is important to remember that while the concentration of sodium in 0.9% saline is 10% higher than that in plasma, the concentration of chloride is 50% higher. The commonest cause of hypochloraemic alkalosis is loss of gastric juice (with its high HCl content) by vomiting or gastric aspiration. This is the main indication for giving 0.9% saline rather than a balanced electrolyte solution.

Chloride excess can also result in renal vasoconstriction, reduced renal blood flow and decreased glomerular filtration rate, leading to decreased urinary sodium and water excretion, and tissue oedema[55,56,121]. However, it has been suggested that adverse effects only occur when the serum chloride concentration exceeds 108 mmol/L[122].

POTASSIUM (K^+)[117]

The total body potassium is between 3000 and 3500 mmol (66-82 g) and is contained largely in the intracellular space where it is the chief cation at a concentration of 120-145 mmol/L, balancing the negative charges on proteins and other non-diffusible anions. Only a very small proportion is in the ECF, where its concentration lies crucially in the narrow range of 3.5-5.3 mmol/L. The balance of potassium

across the cell membrane is maintained by the sodium pump combined with the Gibbs-Donnan equilibrium as described in **Chapter 1**. The normal daily requirements are 1 mmol/kg body weight. The following points are of clinical importance:

- Hyperkalaemia: the serum potassium concentration rises with renal failure and catabolic states, e.g. the response to injury. During the flow phase of injury, as glycogen and protein are broken down, potassium linked to them is released from the cells into the ECF. Conversely, during the convalescent or anabolic phase of injury, the cells take up potassium again as glycogen and protein are resynthesised, causing a fall in ECF potassium concentration. Serum potassium concentrations also rise in response to internal haemorrhage or tissue damage, e.g. muscle necrosis, as potassium is released from dead or dying cells. If AKI and a catabolic state are combined, serum potassium concentrations rise rapidly to dangerous levels, usually accompanied by a metabolic acidosis.

  A rise in concentration above 6.0 mmol/L risks cardiac arrest and any increase above 5.5 mmol/L necessitates urgent treatment. With fluid depletion and pre-renal AKI, intravenous fluids may be sufficient, but additional treatment includes bicarbonate as well as insulin and glucose, both of which drive potassium back into the cells, but only temporarily (4-6 hours). This is a useful emergency measure which may need repeating. Calcium gluconate also helps to stabilize the heart. If these measures fail or oliguria persists, then calcium resonium rectally or renal replacement therapy should be carried out without delay. (see **Chapter 10**).

ECG monitoring in hyperkalaemia

While the ECG findings in hyperkalaemia can usually be correlated with the serum potassium concentration, potentially life-threatening arrhythmias can occur without warning.

- Mild (5.5 – 6.5 mmol/L)
  - Tall 'tented' T waves (seen across the precordial leads) (**Fig. 14.1**)
    Prolonged PR segment
- Moderate (6.5 – 7.5 mmol/L)
  - Decreased or 'flattened' P wave

Prolonged QRS complex

- Severe (>7.5 mmol/L)
  - Progressive widening of the QRS complex
    Axial deviation and bundle branch blocks

The progressively widened QRS eventually merges with the T wave, forming a sine wave pattern. Ventricular fibrillation or asystole may follow.

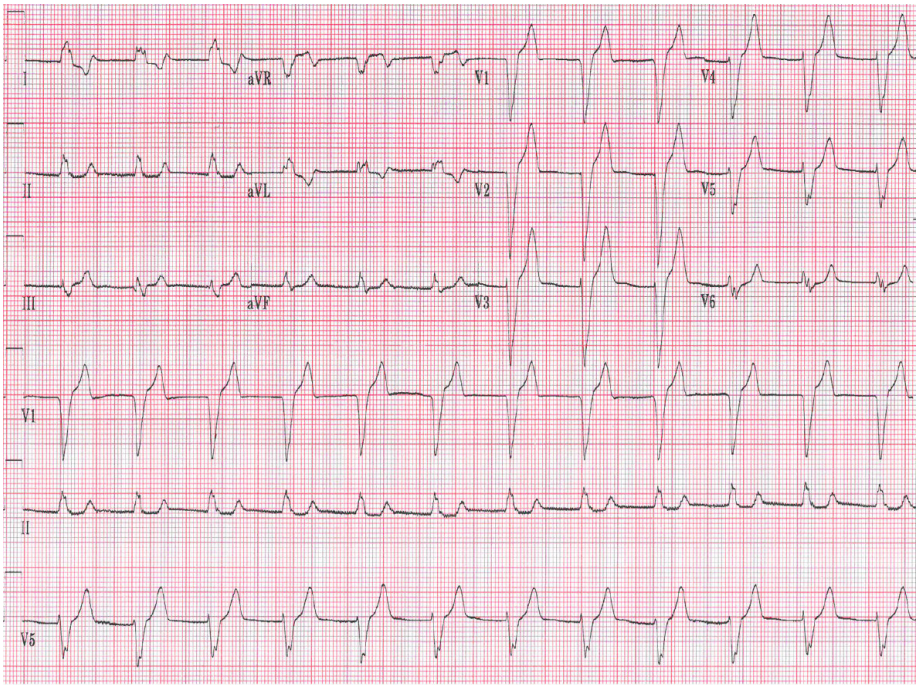


Fig. 14.1 (a): ECG in a patient with hyperkalaemia showing prolonged PR interval, widened QRS complexes and tall peaked T waves.

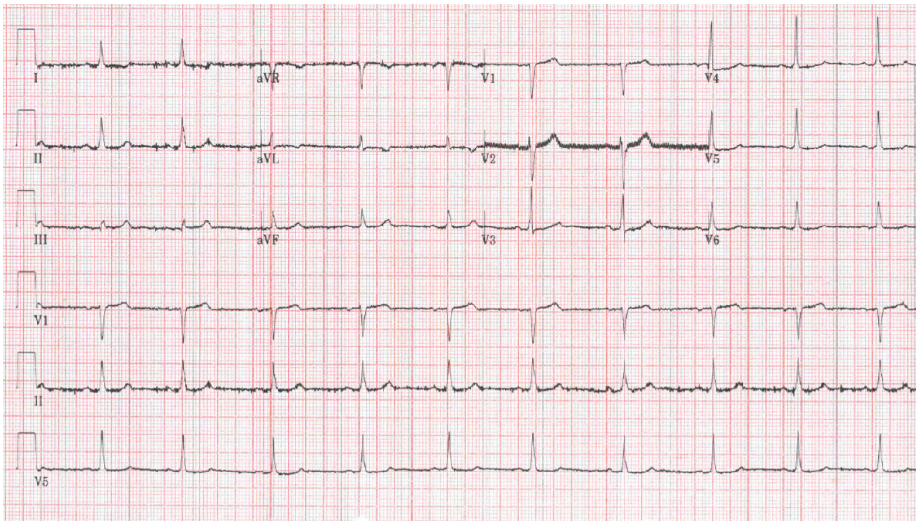


Fig. 14.1 (b): ECG after correction of hyperkalaemia by dialysis.

- **Hypokalaemia**: a fall in serum concentrations below 3.5 mmol/L nearly always reflects potassium deficiency and is usually accompanied by alkalosis because of the interchange of K^+, Na^+, and H^+ in the distal tubule but, with renal tubular defects and laxative abuse, acidosis may be present. Although the relationship between the degree of hypokalaemia and the total potassium deficit is not a precise one, in general it takes a loss of 200-400 mmol to reduce the serum potassium concentration from 4.0 to 3.0 mmol/L and a further loss of the same amount to reduce it to 2.0 mmol/L.

  Symptoms include muscle weakness and, in more severe cases, as serum potassium falls below 2.5 mmol/L, paralysis and cardiac arrhythmias. The most common causes of hypokalaemia are gastrointestinal fluid loss and diuretic therapy. It should also be remembered that patients with diabetic keto-acidosis may have a deficit in excess of 400 mmol even though at presentation the serum potassium concentration may be high due to catabolism, acidosis and pre-renal AKI from fluid loss. As the acidosis is corrected and insulin is given, potassium moves rapidly back into the cells and serum potassium concentrations plunge to dangerous levels unless adequate potassium replacement is given (see **Chapter 13**). A similar phenomenon is seen with the refeeding syndrome (see **Chapter 15**).

  Immediate treatment of hypokalaemia should be aimed at raising the serum potassium concentration to a safe level above 3.0 mmol/L rather than correcting the whole deficit, which can then be done more slowly over the next few days. With mild hypokalaemia (3-3.4 mmol/L), oral supplements at an initial dose of 60-80 mmol/day should be tried, although many patients find oral supplements difficult to tolerate. Potassium chloride is preferred in order to provide chloride to correct any accompanying alkalosis. The more easily tolerated effervescent potassium preparations provide undesirable bicarbonate in the presence of alkalosis, although these may be helpful in the presence of the less severe acidosis.

  In the presence of alkalosis, the distal tubules continue to excrete potassium in exchange for H^+ even in the face of a potassium deficit. In long-term diuretic therapy, a potassium-sparing diuretic or spironolactone should be added to prevent recurrence. In more severe cases, i.e. serum potassium <3.0 mmol/L, it is usually necessary to give KCl in saline intravenously. This also provides extra chloride to correct alkalosis. The use of dextrose as a vehicle risks lowering serum K^+ still further as it stimulates insulin secretion and a combination of insulin and glucose drives potassium into the cell. In general, intravenous KCl should not be given faster than 10-20 mmol/h, although higher rates may need to be given to patients with severe hypokalaemia causing paralysis and arrhythmias. Rates as high as 40-100 mmol/h have been given under these circumstances but this should only be done via a central line under high dependency supervision with ECG and biochemical monitoring.

  ECG monitoring in hypokalaemia

  Typical ECG changes in mild hypokalaemia include flattening and inversion of T waves. In more severe hypokalemia there is prolongation of the Q-T interval, a visible U wave and mild ST depression (**Fig. 14.2**). The QU interval may also be prolonged. Severe hypokalemia can cause arrhythmias such as ventricular tachycardia.

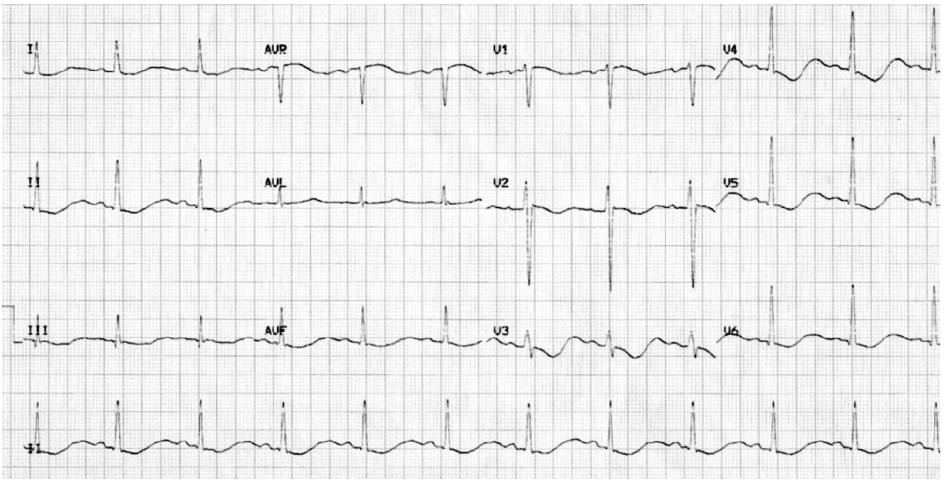


Fig. 14.2: ECG in a patient with hypokalaemia showing ST depression and T wave inversion prominent U waves and long QU interval.

CALCIUM (Ca^{2+})[116]

There are 33,000 mmol (1300 g) in the body, 99% being in bone and only 1% being freely exchangeable. The normal serum concentration is 2.2-2.6 mmol/L, all except 0.8-1.24 mmol/L being bound to protein, chiefly albumin. With falls in serum albumin due to illness and dilution with intravenous fluids, the measured serum Ca^{2+} should be corrected upwards by 0.02 mmol/L for every 1 g/L fall in serum albumin between 40 and 25 g/L. Calcium plays a vital role, not only in bone, but also in neural conductivity, muscular conduction and many other physiological and metabolic processes.

Calcium absorption, excretion and serum concentration are governed by parathyroid hormone, calcitonin, and Vitamin D. Under normal circumstances 240 mmol/day of calcium are filtered by the kidney, with all but 2-10 mmol being reabsorbed. Although some vitamin D is derived from food, most is formed in the skin under the influence of sunlight. It is then hydroxylated in the liver and subsequently the kidney to its most active form $1,25(OH)_2D3$.

Four common aspects of calcium disorders deserve a mention here:

- **Osteomalacia**: This is due to Vitamin D deficiency caused by lack of exposure to sunlight, malnutrition, some gastrointestinal diseases which cause fat malabsorption, and CKD causing reduced levels of $1,25(OH)_2D3$. It is characterised by typical radiological changes in bone, low serum calcium, raised serum phosphate, elevated alkaline phosphatase and parathormone, and low blood vitamin D concentrations. Treatment is with 0.25-1 μg of 1α hydroxycholecalciferol daily and, in some cases, calcium supplements.
- **Osteoporosis**: This involves not only thinning of bone calcium but also of its protein matrix. Its causes are multifactorial but include ageing, the menopause, immobility, calcium deficiency and hypogonadism. It is diagnosed radiologically and by bone density measurement. It may be reduced by sex

hormone replacement, calcium and vitamin D supplements, and exercise, and treated by bisphosphonates.

- **Hypercalcaemia**: Any elevation of serum calcium concentration should be investigated thoroughly. Although, in severe cases it may be important to reduce very high levels of calcium as soon as possible, the main challenge to the doctor is to distinguish early between malignant causes, e.g. myeloma, secondary malignancy in bone, or parathormone secreting tumours, and more easily curable 'benign' causes such as hyperparathyroidism, vitamin D intoxication and sarcoidosis. Primary hyperparathyroidism and functional parathyroid tumours are associated with elevated parathormone concentrations whereas these are suppressed in secondary malignancy from non-parathormone secreting tumours.
- **Mild hypercalcaemia**, i.e. <3.0 mmol/L is usually asymptomatic, is often due to hyperparathyroidism, and may require no active intervention other than monitoring. More severe hypercalcaemia, i.e. ≥3.0 mmol/L is usually symptomatic in proportion to the magnitude and rapidity of rise in the serum calcium concentration. Symptoms include polyuria (due to inhibition of ADH action on the renal tubule), weakness, depression, drowsiness, lethargy, and even coma. It also causes constipation, nausea, vomiting, anorexia and peptic ulcer. Prolonged hypercalcaemia may also result in renal stones and nephrocalcinosis causing CKD. Fluid loss from polyuria may cause pre-renal AKI and a further rise in serum calcium concentration.

  Treatment depends on the severity of the condition, but consists firstly of intravenous saline or a calcium-free balanced crystalloid such as Plasma-Lyte 148, which may of itself be sufficient to reduce the serum calcium concentration. A loop diuretic may be added and, in severe cases, a bisphosphonate given in at least 500 ml of fluid over 4 hours to avoid nephrotoxicity. Etidronate, 7.5 mg/kg can be given daily in this fashion for 3-7 days with careful monitoring of the serum calcium to avoid overshoot hypocalcaemia. Description of the use of other drugs, long-term treatment, and the indications for surgery may be found in appropriate reference works.
- **Hypocalcaemia**: This is usually caused by vitamin D deficiency or hypoparathyroidism, but there are other causes such as CKD and acute pancreatitis. It can also be secondary to hypomagnesaemia, which inhibits parathormone secretion; so in all cases of hypocalcaemia, the serum magnesium should also be measured. Falsely low concentrations of total serum calcium due to hypoalbuminaemia should be excluded (see above).

  Symptoms include neuromuscular irritability causing paraesthesiae, tetany and convulsions. A prolonged QT interval on the ECG may progress to ventricular fibrillation or heart block.

  Treatment depends on its severity and cause, but may involve vitamin D replacement in the form of 1-α cholecalciferol and/or calcium supplements by the oral or intravenous routes. Symptomatic hypocalcaemia should be treated urgently with infusion of 3.75 mmol/kg of elemental calcium (in the form of calcium gluconate) over 4–6 h which will raise the total serum calcium concentration by 0.5–0.75 mmol/L.

MAGNESIUM (Mg^{2+})[118]

This is distributed mainly in bone (500-600 mmol, 12-14.5 g) and the ICF (500-850 mmol). Only 12-20 mmol are in the ECF at any given time, at a concentration of 0.8-1.2 mmol/L. It is an important compo-

nent of many enzyme systems and helps maintain cell membrane stability. The following facts are important to remember.

- Magnesium, like calcium, is bound to albumin and a low serum concentration should be interpreted in the light of the prevailing albumin concentration.
- Magnesium concentration in gastrointestinal fluid varies according to the distance along the intestine. In the proximal small bowel fluid it is only present at 1 mmol/L, whereas in the distal small bowel it rises to higher concentrations. Significant hypomagnesaemia is, therefore, more likely to occur from chronic diarrhoea or from distal stomas or fistulae rather than from more proximal gastrointestinal losses. Gastrointestinal losses are the most common cause of hypomagnesaemia in clinical practice.
- Hypomagnesaemia causes blood parathormone concentrations to fall, resulting in secondary hypocalcaemia. In all cases of hypocalcaemia, therefore, the serum magnesium concentration should be measured. Replacement of magnesium deficits restores parathormone secretion and hence calcium concentrations to normal[73].
- Overt symptoms of hypomagnesaemia, with neuromuscular irritability, convulsions, and arrhythmias are not usually apparent until the serum magnesium concentration falls below 0.4 mmol/L, although with milder degrees of hypomagnesaemia patients may experience improved well-being with adequate replacement, suggesting that even mild hypomagnesaemia may cause sub-clinical symptoms.
- In mild cases of hypomagnesaemia, oral replacement may be sufficient, using magnesium oxide or glycerophosphate. However, magnesium salts are not well absorbed, and in more severe cases it may be necessary to give as much as 160 mmol of magnesium sulphate intravenously in saline over 48 hours to restore normal concentrations. In patients undergoing intravenous feeding for gastrointestinal failure, daily requirements are 8-12 mmol (see **Chapter 15**). An alternative method of replacement, which we have found extremely effective in restoring and maintaining magnesium concentrations, as well as replacing salt and water losses, is to give magnesium sulphate in 0.9% saline subcutaneously (hypodermoclysis) at a concentration of 6-12 mmol/L in up to 2 litres over 4-6 hours every day[73]. This is particularly useful in the short bowel syndrome or inflammatory bowel disease and can be readily administered at home by patients or their carers.

PHOSPHATE (PO_4^{2-})[118]

This is an important constituent of food, the normal intake being 8.5-15 mmol/day (800-1400 mg). Most is in the ICF, and the normal serum concentration lies between 0.8 and 1.5 mmol/L. Severe hypophosphataemia (<0.32 mmol/L) such as may occur acutely in the refeeding syndrome (see **Chapter 15**) or chronically in diseases of bone and mineral metabolism, risks symptoms of myopathy, dysphagia, ileus, respiratory failure, impaired cardiac contractility and encephalopathy. Severe cases may necessitate cautious intravenous administration of 300-500 ml of Phosphate Polyfusor (Fresenius Kabi, 100 mmol PO_4^{2-}, 19 mmol K^+ and 162 mmol Na^+/L) or 30-50 mmol of PO_4^{2-} in 1 litre 0.9% saline over 6-12 hours with frequent monitoring of serum phosphate and other electrolyte concentrations. Excessive or too rapid intravenous administration risks precipitating acute hypocalcaemia and deposition of calcium in soft tissues. Less severe cases can be treated orally with 1 g/day phosphate (e.g. Phosphate-Sandoz) replacement.

Chapter 15: REFEEDING SYNDROME

INTRODUCTION

Refeeding syndrome is an important condition of insidious onset, which may be lethal or cause serious morbidity[123-126]. All patients suffering from weight loss or a period of starvation are potentially liable to develop this condition if given large amounts of nutrients, particularly carbohydrate, too rapidly. This is true whether the nutrients are administered orally, enterally or intravenously. The greater the degree of malnutrition or length of starvation, the greater the risk. Even dextrose containing solutions may precipitate it, if they are administered in large amounts over long periods.

The condition has several components, which may occur separately or in combination. These are hypokalaemia, hypophosphataemia, hypomagnesaemia, oedema, and acute thiamine deficiency causing irreversible brain damage from Wernicke's encephalopathy. It is important to identify patients at risk and take prophylactic measures, rather than waiting until the condition has developed and then trying to treat it.

HYPOKALAEMIA <3.5 mmol/L: (normal range 3.5-5.3 mmol/L)

Potassium reserves may already be reduced in patients suffering from malnutrition, but carbohydrate administration in any patient stimulates insulin secretion and drives potassium from the ECF to the ICF where it is linked to glycogen. Similarly, protein synthesis obliges the cellular uptake of potassium. Particularly in those with diminished potassium reserves, refeeding may precipitate a sufficient degree of hypokalaemia to cause muscle weakness and/or cardiac arrhythmias. Any patient at risk or who is receiving dextrose containing solutions for prolonged periods should be receiving potassium supplements and having their serum potassium concentrations measured at the outset and monitored daily.

HYPOPHOSPHATAEMIA <0.7 mmol/L: (normal range 0.8-1.5 mmol/L)

Exactly the same considerations apply as for hypokalaemia. Since glucose taken up by cells undergoes phosphorylation, carbohydrate administration may precipitate hypophosphataemia. This has been reported in patients receiving intravenous dextrose solutions for several days and can result in decreased respiratory, cardiovascular and neuromuscular function. Symptoms include paraesthesiae, muscular weakness and confusion, sometimes progressing to convulsions and coma. The daily requirement for phosphate is about 20 mmol and prevention of hypophosphataemia can usually be achieved by giving 10 mmol of phosphate for every 1000 kcal that the patient receives. Remember 1 litre of 5% dextrose contains 50 g of carbohydrate with an approximate energy value of 200 kcal.

SALT AND WATER BALANCE

Malnutrition, like the response to injury, is associated with a reduced capacity to excrete a salt and water load. Malnourished patients are, therefore, at risk of developing oedema (famine oedema) from salt and water retention during refeeding. The intake of salt and water in such patients should, therefore, be restricted to that which maintains zero balance. This should be monitored by daily weighing and

serum biochemistry. In a small thin patient for example, water intake for maintenance may be as little as 1 litre per day. Initial sodium intake may also need to be reduced below the normal requirements of 1 mmol/kg/day. On the other hand, any deficit in salt and water balance should be corrected carefully.

THIAMINE DEFICIENCY

Severely malnourished patients as well as those who consume alcohol in excess are particularly liable to this complication as they already have low thiamine reserves. Since thiamine is a cofactor in carbohydrate metabolism, refeeding may precipitate symptoms of thiamine deficiency including confusion, cerebellar signs with nystagmus, and peripheral neuropathy (Wernicke's encephalopathy). As these changes are irreversible once established, identification of patients at risk and provision of prophylactic treatment are vital. Prevention may be achieved by giving 200 mg of thiamine intravenously prior to refeeding, followed by 300 mg daily by mouth or 100 mg intravenously. Thiamine deficiency may also present as wet beri-beri with heart failure.

HYPOMAGNESAEMIA, mild 0.5-0.6 mmol/L, severe <0.4 mmol/L: (normal range 0.8-1.2 mmol/L)

Magnesium, being involved in the formation of adenosine triphosphate (ATP) is taken up by cells during refeeding. Deficiency can cause muscle weakness, cardiac arrhythmias, and hypocalcaemia by reducing parathormone levels. It is not necessary in most cases to give prophylaxis unless there is prior magnesium deficiency, e.g. in short bowel syndrome. Monitoring magnesium concentrations in patients at risk and giving supplements if concentrations fall below 0.7 mmol/L is usually sufficient. Daily requirements are 0.2 mmol/kg/d intravenously or 0.4 mmol/kg/d orally. If magnesium concentrations fall below 0.5 mmol/L then give 24 mmol Mg^{2+} as $MgSO_4$ intravenously over 24 hours.

CONCLUSION

It is important to be aware that the refeeding of patients suffering from weight loss or starvation can precipitate dangerous metabolic changes including hypokalaemia, hypophosphataemia, hypomagnesaemia, acute thiamine deficiency with Wernicke's encephalopathy and oedema secondary to salt and water retention. The risks of developing refeeding syndrome can be avoided by appropriate monitoring and prophylactic supplementation with potassium, phosphate, magnesium and thiamine, and avoidance of salt and water overload.

Chapter 16: PERIOPERATIVE FLUID THERAPY AND OUTCOMES

Although intravenous fluids are the most frequently used "drug" in elective surgical practice, their prescription is often left to the most junior members of the surgical team who may have little knowledge of or training in the subject[127-129]. Perioperative fluid therapy has a major bearing on surgical outcome. Great care is needed in the prescription of fluids administered in the pre-, intra- and postoperative periods if complications and adverse outcomes are to be avoided[130].

There is a relatively narrow margin of safety in perioperative fluid therapy and either too much or too little can have a negative effect on physiological processes and clinical outcome[52,66,131] (**Fig. 16.1**). The goal of perioperative intravenous volume therapy should be to maintain tissue perfusion and cellular oxygen delivery, while at the same time keeping the patient in as near zero fluid and electrolyte balance as possible.

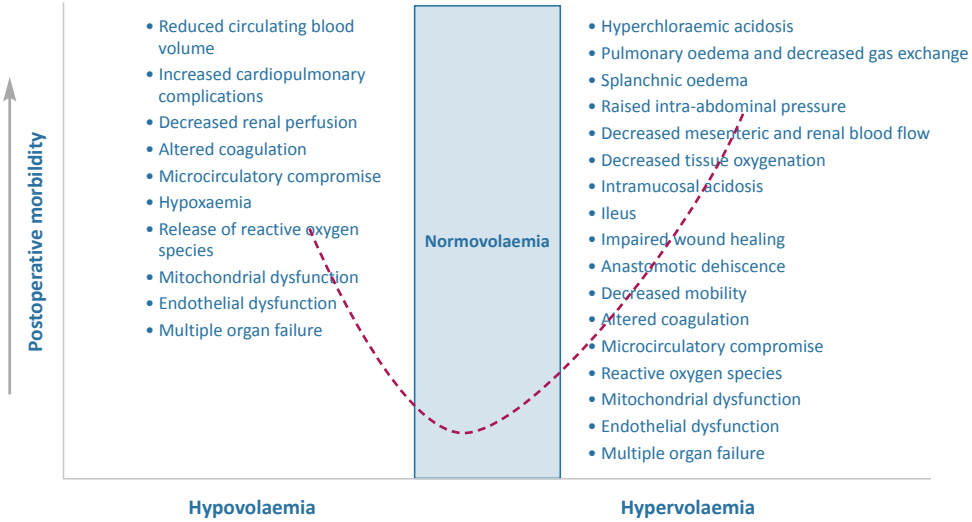


Fig. 16.1: The U-shaped dose-response curve for fluid therapy showing the adverse effects of too much or too little fluid.

PREOPERATIVE PERIOD

Patients should reach the anaesthetic room in a state as close to euvolaemia as possible with any preoperative fluid and electrolyte imbalance having been corrected. Pre-existing comorbidities must be considered when assessing fluid status. Prolonged periods of preoperative fasting cause patients to reach the anaesthetic room in a state of fluid depletion, which may be further compounded by unnecessary bowel preparation. Current anaesthetic recommendations that allow patients to eat for up to

6 h and drink clear fluids up to 2 h prior to the induction of anaesthesia help to prevent preoperative fluid depletion without increasing aspiration-related complications[132]. In those instances when mechanical bowel preparation is indicated, patients may lose up to 2 L of total body water as a consequence[133], and fluid and electrolyte derangements may occur even if patients are permitted oral fluids. Some of these patients, therefore, may require appropriate intravenous fluid therapy to compensate for these deficits[134]. It has recently been shown that withholding oral fluids for prolonged periods prior to the induction of anaesthesia can result in intraoperative hypotension and adverse events[135].

On the other hand, the practice of prescribing volumes of salt containing fluids in excess of requirements during the preoperative period causes salt and water overload which also has adverse effects on surgical outcome.

INTRAOPERATIVE PERIOD

The aim of intraoperative intravenous fluid therapy is to maintain intravascular volume, cardiac output and tissue perfusion whilst avoiding salt and water overload. Most patients require crystalloids (see **Chapters 6** and **7**) at a rate of 1-4 ml/kg/h to maintain homeostasis[77]. However, some patients develop intravascular volume deficits which require correction by administration of goal-directed boluses of intravenous solutions (usually a colloid). Goal directed fluid therapy (GDFT) is aimed at maintaining intravascular normovolaemia guided by changes in stroke volume as measured by a minimally invasive cardiac output monitor to optimize the position of each patient on his/her individual Frank–Starling curve[136,137]. In addition to the background crystalloid infusion, fluid boluses (200-250 ml) should be given to treat any objective evidence of hypovolaemia (>10% fall in stroke volume) in order to optimise intravascular volume and cardiac output[138]. A recent meta-analysis that included 23 studies with 2099 patients has shown that GDFT was associated with a significant reduction in morbidity, hospital length of stay, intensive care length of stay, and time to passage of faeces[139]. However, when patients were managed within enhanced recovery after surgery (ERAS) pathways, with optimal perioperative care and avoidance of postoperative fluid overload, the only significant reductions were in intensive care length of stay and time to passage of faeces. Hence, within ERAS programmes, it may not be necessary to offer all patients GDFT[140], which should be reserved for high-risk patients or for patients undergoing high risk procedures[77].

POSTOPERATIVE PERIOD

For most patients undergoing elective surgery intravenous fluid therapy is usually unnecessary beyond the day of operation, except for those undergoing upper gastrointestinal and pancreatic procedures. With these exceptions, patients should be encouraged to drink as soon as they are awake and free of nausea after the operation. An oral diet can usually be started on the morning after surgery[141,142]. When adequate oral fluid intake is tolerated, intravenous fluid administration should be discontinued and be restarted only if required to maintain fluid and electrolyte balance. If intravenous fluids are required, then in the absence of ongoing losses, only maintenance fluids should be given at a rate of 25-30 ml/kg/day with no more than 70-100 mmol sodium/day, along with potassium supplements (up to 1 mmol/kg/day)[130]. As long as this volume is not exceeded, hyponatraemia is very unlikely to occur despite the provision of hypotonic solutions[57,143]. Any ongoing losses (e.g. vomiting or high stoma losses) should be replaced on a like for like basis, in addition to maintenance requirements. After ensuring the patient is normovolaemic, hypotensive patients receiving epidural analgesia should be treated with

vasopressors rather than indiscriminate fluid boluses[144,145]. Fluid deficit or overload of as little as 2.5 L[9] can cause adverse effects in the form of increased postoperative complications, prolonged hospital stay and higher costs due to increased utilisation of resources[66,146,147].

However, it has not been unusual in the past for patients to receive in excess of 5 L water and 700 mmol sodium (and chloride)/day in the early postoperative period. Most of the retained fluid after such infusions accumulates in the interstitial compartment, leading to oedema if overload exceeds 2-3 L. An excess of 0.9% saline in such cases causes hyperosmolar states, hyperchloraemic acidosis[11,50,51,148-150], and decreased renal blood flow and glomerular filtration rate, which in turn exacerbates sodium retention[55,56]. Oedema impairs pulmonary gas exchange and tissue oxygenation leading to an increase in tissue pressure in organs such as the kidney which are surrounded by a non-expansible capsule. Microvascular perfusion is compromised, arterio-venous shunting increases and lymphatic drainage is reduced, leading to further oedema (**Fig. 16.2**). Hyperchloraemic acidosis, as a result of saline infusions has been shown to reduce gastric blood flow and decrease gastric intramucosal pH in elderly surgical patients (see **Chapter 2**), and both respiratory and metabolic acidosis have been associated with impaired gastric motility. Fluid overload also causes splanchnic oedema resulting in increased abdominal pressure, ascites and even the abdominal compartment syndrome, which may lead to decreased mesenteric blood flow and ileus, with delayed recovery of gastrointestinal function, an increase in gut permeability, intestinal failure and even anastomotic dehiscence (**Fig. 16.3**)[151,152].

Metabolic	• Hyperchloroemic acidosis • ↑ need for buffers to correct acidosis
Body water	• Possible damage to the endothelial glycocalyx • ↑ interstitial fluid volume leading to oedema
Renal	• Renal oedema and capsular stretch leading to intrarenal tissue hypertension • Renal vascoconstriction, ↓ renal blood flow and renal tissue perfusion • ↓ glomerular filtration rate, urine volume and sodium excretion
Gastrointestinal	• Gastrointestinal oedema, intestinal stretch • Ileus, impaired anastomotic healing
Haematological	• ↑ intraoperative blood loss • ↑ need for blood product transfusion
Clinical outcomes	• ↑ postoperative complications • ↑ mortality • ↑ incidence of acute kidney injury and need for renal replacement therapy

Fig. 16.2: The adverse effects of hyperchloraemia.

Fluid restriction resulting in fluid deficit can be as detrimental as fluid excess by causing decreased venous return and cardiac output, diminished tissue perfusion and oxygen delivery and increased blood viscosity. It can also lead to an increase in the viscosity of pulmonary mucus and result in mucous plug formation and ateletactasis. Induction of anaesthesia in patients with a fluid deficit further reduces the

effective circulatory volume by decreasing sympathetic tone. Inadequate fluid resuscitation and decreased tissue perfusion can lead to gastrointestinal mucosal acidosis and poorer outcome.

A meta-analysis of patients undergoing major abdominal surgery has shown that patients managed in a state of near-zero fluid and electrolyte balance had a 59% reduction in risk of developing complications when compared with patients managed in a state of fluid imbalance (deficit or excess). There was also a 3.4-day reduction in hospital stay in the near-zero fluid balance group[66].

A recent randomised clinical trial that studied intraoperative and day 1 postoperative fluid therapy[153], however, showed that a restrictive fluid regimen was not associated with a higher rate of disability-free survival than a liberal fluid regimen. In addition, there was a higher rate of AKI in patients who received a restrictive fluid regimen. However, it should be highlighted that the authors did not record fluid balance after day 1 and that weight gain was 0.3 kg in the restrictive group and 1.6 kg in the liberal group. This is below the 2.5 kg weight gain that is the threshold for producing oedema and complications[9]. In addition, there was no record of fasting, oral fluids and food consumption. Hence, it may be concluded that a modestly liberal administration of balanced salt solutions does not create substantial fluid retention and that it may be safer than a truly restrictive regimen.

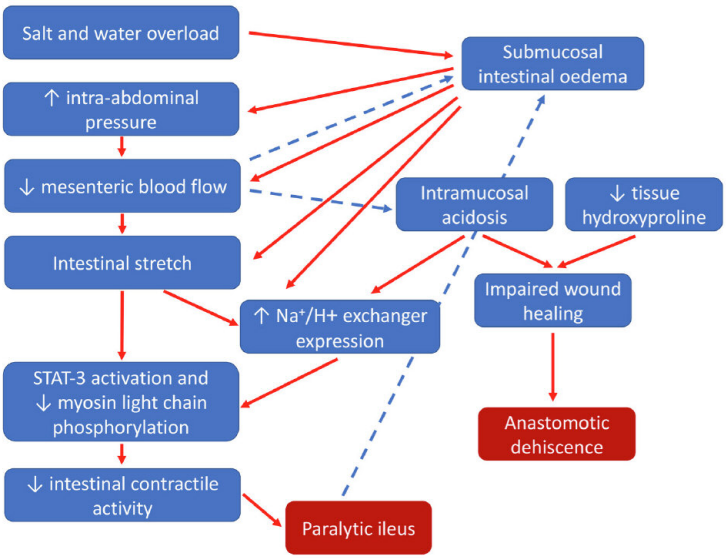


Fig. 16.3: Fluid overload and the intestine. STAT-3 = signal transducer and activation of transcription-3. (Modified and redrawn from Chowdhury and Lobo[151]).

BALANCED CRYSTALLOIDS vs. 0.9% SALINE

As described above, there is considerable evidence from physiological studies that large volumes of intravenous 0.9% saline cause hyperchloraemic acidosis, interstitial fluid overload, impairment of renal blood flow and glomerular filtration with a consequent reduction in urinary water and sodium excretion[51,55,56,121,150,154].

A large observational, propensity-matched study in patients undergoing surgery has suggested that 0.9% saline, because of its high chloride content, may be harmful, especially to the kidney when compared with a balanced crystalloid[155]. Another propensity-matched study has suggested that up to 22% of patients develop acute hyperchloraemia (>110 mmol/L) in the postoperative period and that this is associated with an increased risk of 30-day mortality and longer length of stay than those who do not develop hyperchloraemia[156]. However, as there are no large-scale randomised trials comparing 0.9% saline with balanced crystalloids in a surgical population, the current evidence cannot be regarded as high quality. In addition, a recent meta-analysis that was limited by imprecision and studies of a small sample size has shown that for unselected critically ill or perioperative adult patients there was no evidence of benefit from low- versus high-chloride solutions[157]. However, because of the observed undesirable effects of 0.9% saline, we suggest the use of more physiological balanced crystalloids, except where there is specific chloride deficiency.

MANAGEMENT OF POSTOPERATIVE OLIGURIA

Oliguria in the adult is usually defined as a urine output <0.5 ml/kg/h, or <500 ml in 24 h (See **Chapter 9**). However, urine output and oliguria alone are not reliable indicators of intravascular volume deficit in the first 48 h after surgery as the postoperative metabolic response leads to salt and water retention[158]. Oliguria should be assessed carefully and should only be treated with additional intravenous fluids if there is clear evidence of intravascular hypovolaemia (e.g. tachycardia, hypotension, sweating, confusion, decreased capillary return, etc.), as excessive fluid administration has been associated with AKI[88,159]. If there are no clinical signs of intravascular hypovolaemia, it is useful to average urine output over the previous 4 hours rather than rely on a single hourly value, before reconsidering the need for additional fluid. A conservative fluid regimen does not appear to increase the risk of postoperative oliguria or AKI[147,160-162]. Unnecessary additional intravenous fluids or diuretics do not improve renal function or protect against AKI[159-161,163].

The algorithm in **Fig. 16.4** outlines a practical approach to applying the above principles to fluid provision in elective surgery.

CONCLUSION

Perioperative fluid therapy has a major effect on postoperative outcomes. If complications are to be avoided, patients should be managed in as near a state of “zero fluid balance” as possible as both fluid overload and deficit can lead to complications. Accurate management of fluid balance forms an important part of ERAS programmes, which have done so much to improve surgical outcome and shorten hospital stay. Moore and Shires[164] wrote in 1967, “The objective of care is restoration to normal physiology and normal function of organs, with a normal blood volume, functional body water and electrolytes. This can never be achieved by inundation.” This recommendation has never been bettered.

Preoperative

- Ensure adequate hydration by letting patients drink clear fluids up to 2 h before induction of anaesthesia
- Avoid mechanical bowel preparation
- Patients with ongoing losses (e.g. enterocutaneous fistulae) should have fluid losses replaced adequately before being sent to theatre

Intraoperative

- Avoid excessive fluid administration
- Balanced crystalloids preferred to 0.9%saline
- Optimise stroke volume and cardiac output and reduce stroke volume variation in high-risk patients bv administering small fluid boluses (200-250 ml) in response to data obtained from intraoperative monitoring (e.g. transoesophageal Doppler, lithium dilution or pulse contour analysis)
- Give blood transfusion and blood products when appropriate

Postoperative

- Avoid excessive fluid administration
- Try and achieve a state of near-zero fluid balance (most patients do not need more than 2-2.5 L water, 70-100 mmol sodium and 50-70 mmol potassium per day)
- Early resumption of oral fluid/diet (achieved in most patients by postoperative day 1 or 2)
- In patients with inadequate oral intake, supplement with intravenous fluids avoiding excess.
- Consider enteral nutrition if unable to eat (parenteral nutrition in cases of intestinal failure)

Fig. 16.4: Suggested algorithm for fluid therapy in patients undergoing elective surgery.

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MULTIPLE CHOICE QUESTIONS

Please choose the single best answer.

1. The best measure of water balance is

- ☐ a. Changes in serum sodium concentration
- ☐ b. Accurately maintained fluid balance charts
- ☐ c. Urinary osmolality
- ☐ d. Serial weighing
- ☐ e. Serum creatinine concentration

2. During the flow phase of the metabolic response to injury

- ☐ a. There is a high urinary sodium concentration
- ☐ b. Hypokalaemia is common
- ☐ c. Dangerous hyperkalaemia is common
- ☐ d. There is renal retention of sodium and water
- ☐ e. Urea production rates are decreased

3. The extracellular fluid volume

- ☐ a. Is 30% of body weight
- ☐ b. Increases during short-term fasting
- ☐ c. Is 20% of body weight
- ☐ d. Consists of the interstitial fluid only
- ☐ e. Is supported osmotically mainly by albumin

4. In health, albumin leaks from the intravascular space

- ☐ a. At a rate of 5%/h
- ☐ b. At a rate of 10%/h
- ☐ c. At a rate of 15%/h
- ☐ d. At a rate that decreases after surgery
- ☐ e. At a rate that decreases in sepsis

5. Albumin which leaks from the intravascular to the interstitial space

- ☐ a. Returns to the circulation via the veins
- ☐ b. Is catabolised to its constituent amino acids
- ☐ c. Is bound to glucose
- ☐ d. Causes inflammation
- ☐ e. Is returned to the circulation via the lymphatics

6. In diabetic ketoacidosis

- ☐ a. Treatment should be delayed until investigations are completed
- ☐ b. Crystalloids should be infused without delay

☐ c. The blood sugar should be lowered with insulin as rapidly as possible
☐ d. As the blood sugar falls, serum sodium concentration also falls
☐ e. Hypokalaemia is common

7. A fall in serum sodium concentration most commonly denotes

☐ a. A negative sodium balance
☐ b. A positive water balance
☐ c. Acute kidney injury
☐ d. Hypoaldosteronism
☐ e. Congestive heart failure

8. A serum potassium concentration >6 mmol/L

☐ a. Requires no action other than further monitoring
☐ b. Is common in the early postoperative period
☐ c. Risks cardiac arrest
☐ d. Is commonly associated with diuretic treatment
☐ e. Is suggestive of the syndrome of inappropriate antidiuretic hormone secretion

9. The strong ion difference of 0.9% saline solution is

☐ a. 0 mmol/L
☐ b. 154 mmol/L
☐ c. 30 mmol/L
☐ d. 308 mmol/L
☐ e. -10 mmol/L

10. A common presenting feature of hyperglycaemic hyperosmolar nonketotic state is

☐ a. Acidosis
☐ b. Acidaemia
☐ c. Hypokalaemia
☐ d. Negative salt balance
☐ e. Positive water balance

11. The osmolality of 0.9% saline is

☐ a. 308 mOsm/kg
☐ b. 308 mOsm/L
☐ c. 154 mOsm/kg
☐ d. 154 mOsm/L
☐ e. 305 mOsm/kg

12. Hyperchloraemia is associated with

☐ a. A metabolic acidosis
☐ b. A metabolic alkalosis

☐ c. An increase in the strong ion difference
☐ d. Hyponatraemia
☐ e. Increased urine output

13. 6% hydroxyethyl starch
☐ a. Is the fluid of choice for resuscitation of the septic patient
☐ b. Increases the risk of acute kidney injury in critically ill patients
☐ c. Has a greater risk of causing anaphylaxis than gelatins
☐ d. Should be used in a minimum dose of 70 ml/kg/day
☐ e. Should not be used for intraoperative goal directed fluid therapy

14. A feature of the refeeding syndrome is
☐ a. Hyperphosphataemia
☐ b. Hypocalcaemia
☐ c. Hypokalaemia
☐ d. Hypernatraemia
☐ e. Hyponatraemia

15. Infusion of hypotonic solutions can cause
☐ a. Cerebral oedema in neurosurgical patients
☐ b. Hypernatraemia
☐ c. Salt and water retention
☐ d. Acute kidney injury
☐ e. Oliguria

16. An intravenous fluid infusion rate of 41.6 ml/h delivers
☐ a. 1 litre over 36 hours
☐ b. 1 litre over 24 hours
☐ c. 1 litre over 6 hours
☐ d. 2 litres over 24 hours
☐ e. 1 litre over 18 hours

17. The preferred solution for maintenance of fluid balance intravenously is
☐ a. 0.9% saline
☐ b. 4% dextrose in 0.18% saline with added potassium
☐ c. Hartmann's solution
☐ d. 4% gelatin
☐ e. 5% dextrose

18. The flow phase of the metabolic response to injury is characterised by
☐ a. Potassium retention
☐ b. Water diuresis

☐ c. Sodium retention
☐ d. Hyponatraemia
☐ e. Hyperkalaemia

19. A peripheral intravenous cannula should be resited at least
☐ a. Once a week
☐ b. Daily
☐ c. Every 72 hours
☐ d. 12 hourly
☐ e. Once a fortnight

20. Which one of the following statements about the properties of colloids is true?
☐ a. The larger the size of molecules in the colloid solution the longer it is retained in the intravascular compartment
☐ b. The oncotic pressure of the solution is inversely related to the number of molecules in the solution
☐ c. The size of molecules in the colloid solution is inversely related to the half-life of the solution
☐ d. The number of molecules in the colloid solution is inversely related to the half-life of the solution
☐ e. The smaller the size of molecules in the colloid solution the longer it is retained in the intravascular compartment

21. Regarding body fluid compartments
☐ a. Body water comprises 85% of total body weight
☐ b. The extra-cellular water compartment comprises 40% of total body weight
☐ c. The intra-cellular water compartment comprises 20% of total body weight
☐ d. The interstitial fluid compartment is part of the intra-cellular water compartment
☐ e. The intavascular and interstitial fluid concentrations of electrolytes are similar

22. The following is the correct composition (in mmol/L) of Hartmann's Solution:
☐ a. Sodium 131, Potassium 5, Calcium 2, Chloride 111, Lactate 29
☐ b. Sodium 154, Potassium 5, Calcium 2, Chloride 154, Lactate 20
☐ c. Sodium 131, Potassium 3, Calcium 5, Chloride 50, Lactate 29
☐ d. Sodium 154, Potassium 2, Calcium 2, Chloride 154, Lactate 20
☐ e. Sodium 111, Potassium 5, Calcium 2, Chloride 111, Lactate 29

23. The following are required daily in healthy adults:
☐ a. Water 35-55 ml/kg, Sodium 3-4 mmol/kg, Potassium 1-2 mmol/kg
☐ b. Water 25-30 ml/kg, Sodium 1-1.2 mmol/kg, Potassium 1 mmol/kg
☐ c. Water 10 ml/kg, Sodium 1 mmol/kg, Potassium 3 mmol/kg
☐ d. Water 30 ml/kg, Sodium 3 mmol/kg, Potassium 1 mmol/kg
☐ e. Water 35-55 ml/kg, Sodium 1-1.2 mmol/kg, Potassium 3 mmol/kg

24. Which one of the following statements about 0.9% sodium chloride solution ("Normal Saline") is true?

☐ a. 1-Litre contains 90 grams of sodium
☐ b. It contains 131 mmol/L sodium
☐ c. It contains 154 mmol/L chloride
☐ d. It has a pH of 7.5
☐ e. When given in excess it causes a hypochloraemic alkalosis

25. The metabolic response to surgery or trauma causes:

☐ a. Increased urinary loss of sodium, increased urinary loss of potassium, increased urine output
☐ b. Decreased urinary loss of sodium, decreased urinary loss of potassium, increased urine output
☐ c. Increased urinary loss of sodium, increased urinary loss of potassium, decreased urine output
☐ d. Decreased urinary loss of sodium, decreased urinary loss of potassium, water retention, increased urine output
☐ e. Decreased urinary loss of sodium, increased urinary loss of potassium, water retention, decreased urine output

26. The following are characteristics of 1-Litre of 5% Dextrose solution:

☐ a. Sodium 154 mmol, Chloride 154 mmol, Glucose 500 grams, pH 4
☐ b. Sodium 70 mmol, Chloride 70 mmol, Glucose 50 grams, pH 7.5
☐ c. Sodium 0 mmol, Chloride 0 mmol, Glucose 500 grams, pH 7.5
☐ d. Sodium 0 mmol, Chloride 0 mmol, Glucose 50 grams, pH 4
☐ e. Sodium 70 mmol, Chloride 70 mmol, Glucose 50 grams, pH 6

27. The following are constituents of 1-Litre of Dextrose (4%)/Saline (0.18%) solution:

☐ a. Sodium 154 mmol, Chloride 154 mmol, Glucose 40 grams
☐ b. Sodium 31 mmol, Chloride 31 mmol, Glucose 40 grams
☐ c. Sodium 131 mmol, Chloride 131 mmol, Glucose 40 grams
☐ d. Sodium 70 mmol, Chloride 70 mmol, Glucose 400 grams
☐ e. Sodium 131 mmol, Chloride 131 mmol, Glucose 400 grams

28. Injury or inflammation result in:

☐ a. A decrease in capillary permeability and an increase in plasma albumin concentrations
☐ b. A decrease in capillary permeability and an increase in interstitial albumin concentrations
☐ c. An increase in capillary permeability and an increase in plasma albumin concentrations
☐ d. An increase in capillary permeability and a decrease in plasma albumin concentrations
☐ e. No change in capillary permeability and a decrease in plasma albumin concentrations

29. Which of the following fluid prescriptions is most appropriate for a 70-kg man on the first postoperative day after a standard right hemicolectomy:

☐ a. 3-Litres 0.9% Sodium Chloride with a total of 70 mmol Potassium
☐ b. 3-Litres 0.9% Sodium Chloride with a total of 120 mmol Potassium
☐ c. 2.5-Litres 5% Dextrose with a total of 70 mmol Potassium
☐ d. 1-Litre Dextrose saline and 1.5-Litres 0.5% Dextrose with a total of 70 mmol Potassium
☐ e. 2-Litres 4% Dextrose/0.18% Saline with a total of 70 mmol Potassium

30. Which one of the following statements concerning body compartments is true?

☐ a. Sodium is the major intracellular cation
☐ b. Potassium is the major extracellular cation
☐ c. Chloride is the major intracellular anion
☐ d. Sodium is the major extracellular cation
☐ e. Albumin is the major intracellular anion

31. Which of the following statements concerning the anion gap is true?

☐ a. The anion gap always increases in a metabolic acidosis
☐ b. The anion gap is equal to the concentration of (Sodium + Magnesium) – (Chloride + Phosphate)
☐ c. The normal range for the anion gap is 30-40 mmol/L
☐ d. The anion gap always increases in a metabolic alkalosis
☐ e. The anion gap is equal to the concentration of (Sodium + Potassium) – (Chloride + Bicarbonate)

32. Advantages of using colloids include:

☐ a. A larger volume of colloid is required to achieve the same plasma volume expanding effects as crystalloids
☐ b. Colloids protect platelet function
☐ c. There is less risk of anaphylaxis with using colloids
☐ d. Colloids are cheaper to use than crystalloids
☐ e. Smaller volumes of colloid are needed to resuscitate patients (compared with crystalloids)

33. An arterial blood gas profile of pH 7.21, P_aCO_2 6.5 kPa, P_aO_2 15 kPa, Bicarbonate 15 mmol/L, Base Excess -10 mmol/L implies which of the following physiological conditions:

☐ a. Mixed metabolic and respiratory acidosis without compensation
☐ b. Primary metabolic acidosis with respiratory compensation
☐ c. Primary metabolic acidosis without compensation
☐ d. Mixed metabolic and respiratory acidosis with partial compensation
☐ e. Primary respiratory acidosis with metabolic compensation

34. Consequences of excess 0.9% sodium chloride infusion include

- ☐ a. Renal tubular acidosis
- ☐ b. An increase in plasma oncotic pressure
- ☐ c. Metabolic alkalosis
- ☐ d. A decrease in the strong ion difference
- ☐ e. Hyponatraemia

35. Concerning the use of fluids for acute resuscitation of critically ill surgical patients:

- ☐ a. 5% dextrose is the ideal resuscitation fluid
- ☐ b. The aim is to restore intracellular volume
- ☐ c. Larger volumes of hypertonic saline must be used to achieve the same plasma expanding effects as 0.9% saline
- ☐ d. The recommended fluid in daily practice is 20% albumin
- ☐ e. The goal of fluid replacement is to improve microcirculatory perfusion

36. The following statements about central venous pressure (CVP) monitoring are true:

- ☐ a. CVP is directly related to blood volume
- ☐ b. Following a fluid challenge, a persistent rise in CVP implies further volume expansion is required
- ☐ c. CVP is an accurate marker of left-heart function
- ☐ d. CVP is inversely related to blood volume
- ☐ e. Following a fluid challenge, a declining CVP implies further volume expansion is required

37. The average sodium deficit in moderate diabetic ketoacidosis is

- ☐ a. 100-120 mmol
- ☐ b. 500-600 mmol
- ☐ c. 280-350 mmol
- ☐ d. >700 mmol
- ☐ e. <100 mmol

38. The average potassium deficit in severe diabetic ketoacidosis is

- ☐ a. <100 mmol
- ☐ b. 120-220 mmol
- ☐ c. >700 mmol
- ☐ d. 280-350 mmol
- ☐ e. >350 mmol

39. The average sodium deficit in a diabetic patient with hyperosmolar nonketotic state is

- ☐ a. 100-150 mmol
- ☐ b. 150-220 mmol
- ☐ c. 350-700 mmol
- ☐ d. >700 mmol
- ☐ e. <100 mmol

40. Excess salt and water administration

- ☐ a. Is inevitable during fluid resuscitation for shock
- ☐ b. Has little consequence on outcome after surgery
- ☐ c. Improves gastrointestinal function
- ☐ d. Causes oedema when there is a positive fluid balance of 1 L
- ☐ e. Should usually be treated with diuretics

41. In older adults admitted to hospital

- ☐ a. Hyponatraemia is common
- ☐ b. Salt and water excess is more common than deficit
- ☐ c. Hypokalaemia is more common than hyponatraemia
- ☐ d. Fluid balance problems are rare
- ☐ e. Skin turgor is a good marker of fluid balance status

42. Refeeding syndrome

- ☐ a. Is associated with a decrease in serum calcium
- ☐ b. Can lead to irreversible neurological damage
- ☐ c. Is not related to the degree or duration of starvation
- ☐ d. Is caused by excessive energy intake during refeeding and not by excess of any one particular nutrient
- ☐ e. Is easier to treat than prevent

43. Salt and water deficit can cause

- ☐ a. Pre-renal acute kidney injury
- ☐ b. A fall in haematocrit
- ☐ c. Hypokalaemia
- ☐ d. Convulsions
- ☐ e. Hypoparathyroidism

44. Hypomagnesaemia can cause

- ☐ a. Hypercalcaemia
- ☐ b. Muscle rigidity
- ☐ c. Hypoparathyroidism
- ☐ d. Neuromuscular irritability
- ☐ e. Diarrhoea

45. Hypophosphataemia

- ☐ a. Is a feature of the metabolic response to injury
- ☐ b. Can be secondary to hypokalaemia
- ☐ c. Is a feature of the refeeding syndrome
- ☐ d. Can cause hypernatraemia
- ☐ e. Can produce constipation

46. Which of the following is a feature of Stage 1 acute kidney injury?

- ☐ a. Increase in serum creatinine by ≥26 µmol/L within 12 h or increase in serum creatinine ≥1.5-1.9× baseline or a urine output <0.5 ml/kg/h for >2 consecutive hours
- ☐ b. Increase in serum creatinine by ≥26 µmol/L within 24 h or increase in serum creatinine ≥2-2.9× baseline or a urine output <0.5 ml/kg/h for >6 consecutive hours
- ☐ c. Increase in serum creatinine by ≥26 µmol/L within 24 h or increase in serum creatinine ≥1.5-1.9× baseline or a urine output <0.5 ml/kg/h for >6 consecutive hours
- ☐ d. Increase in serum creatinine by ≥26 µmol/L within 24 h or increase in serum creatinine ≥1.5-1.9× baseline or a urine output <0.5 ml/kg/h for >12 consecutive hours
- ☐ e. Increase in serum creatinine by ≥26 µmol/L within 12 h or increase in serum creatinine ≥1.5-1.9× baseline or a urine output <0.3 ml/kg/h for >6 consecutive hours

47. Which of the following is not a cause of intrinsic acute kidney injury

- ☐ a. Ischaemia-reperfusion injury
- ☐ b. Intravenous iodinated contrast media
- ☐ c. Myeloma
- ☐ d. Cholesterol embolisation
- ☐ e. Retroperitoneal fibrosis

48. During the de-escalation phase of the treatment of shock

- ☐ a. Intravenous starches are the treatment of choice
- ☐ b. High dose inotropes may be necessary
- ☐ c. Renal replacement therapy may be necessary to achieve a negative fluid balance
- ☐ d. Fluid replacement volume should be 1 L more than the urine output
- ☐ e. 10 mg frusemide should be added to every litre of 0.9% saline prescribed

49. Chronic kidney disease

- ☐ a. Is defined by an eGFR less than 60 ml/min/1.73m^2, by the presence of markers of kidney damage (structural or albuminuria), or both, for at least 3 months
- ☐ b. The diagnosis of chronic kidney disease requires two serum creatinine values measured at least 180 days apart
- ☐ c. Diabetes mellitus accounts for 10% of all cases of chronic kidney disease
- ☐ d. Treatment should aim to maintain blood pressure <150/90 mm Hg
- ☐ e. Anaemia in advanced chronic kidney disease is commonly due to blood loss

50. Both fluid deficit and fluid overload can result in

- ☐ a. Hyperchloraemic metabolic acidosis
- ☐ b. Raised intraabdominal pressure
- ☐ c. Splanchnic oedema
- ☐ d. Mitochondrial and endothelial dysfunction
- ☐ e. Oculogyric crisis

51. Hyponatraemia is most commonly caused by

- ☐ a. Sodium loss or deficit
- ☐ b. The metabolic response to injury
- ☐ c. Starvation
- ☐ d. Excess water intake
- ☐ e. Antihypertensive drugs

52. ECG changes in hyperkalaemia include all of the following except

- ☐ a. Prominent U waves
- ☐ b. Tall, tented T waves
- ☐ c. Flattened P waves
- ☐ d. Widening of the QRS complex
- ☐ e. Ventricular fibrillation

53. In patients with acute kidney injury, early referral is recommended for all of the following except

- ☐ a. Serum creatinine ≥3 × baseline value
- ☐ b. pH <7.15
- ☐ c. methanol poisoning
- ☐ d. bloody diarrhoea, haemolysis and thrombocytopaenia
- ☐ e. Urine output <0.5 ml/kg/h for 3 consecutive h

54. Hyperchloraemic acidosis can cause all of the following except

- ☐ a. Oliguria
- ☐ b. Increased glomerular filtration rate
- ☐ c. Increased renal afferent arteriolar resistance
- ☐ d. Decreased urinary sodium excretion
- ☐ e. Release of adenosine

55. Which of the following is correct with regards to osmolality?

- ☐ a. It is measured in mOsm/kg
- ☐ b. It is the sum of mmol of ions divided by the volume of fluid
- ☐ c. Osmolality is usually greater than osmolarity
- ☐ d. The osmolality of plasma takes into account albumin concentration
- ☐ e. Lactate is a major contributor to serum osmolality

56. Which of the following can cause metabolic alkalosis?

- ☐ a. Infusion of large volumes of 0.9% saline
- ☐ b. Cushing's syndrome
- ☐ c. Hypovolaemic shock
- ☐ d. Metformin
- ☐ e. Chronic kidney disease

57. Which of the following drugs can raise the serum potassium concentration?

- ☐ a. Insulin
- ☐ b. Angiotensin converting enzyme inhibitors
- ☐ c. Thiazide diuretics
- ☐ d. Salbutamol
- ☐ e. Hydrocortisone

58. The normal anion gap is

- ☐ a. -2 to 2 mmol/L
- ☐ b. 0-3 mmol/L
- ☐ c. 5-11 mmol/L
- ☐ d. 12-17 mmol/L
- ☐ e. 20-25 mmol/L

59. Which of the following body fluid compartments has the largest volume of water?

- ☐ a. The interstitial space
- ☐ b. The intracellular space
- ☐ c. The extracellular space
- ☐ d. The intravascular space
- ☐ e. Lymph

60. Which of the following control water homeostasis?

- ☐ a. Carotid sinus baroreceptors
- ☐ b. Atrial natriuretic peptide
- ☐ c. Brain natriuretic peptide
- ☐ d. Renin-angiotensin-aldosterone system
- ☐ e. Osmoreceptors in the hypothalamus

61. The hour-1 bundle for initial resuscitation for sepsis and septic shock include all of the following except:

- ☐ a. Measuring serum lactate concentration
- ☐ b. Intravenous crystalloid administration @ 30 ml/kg for hypotension
- ☐ c. Start vasopressors in hypotensive patients to maintain systolic blood pressure >100 mm Hg
- ☐ d. Obtaining blood cultures before administering antibiotics
- ☐ e. Administration of broad spectrum intravenous antibiotics

62. Which of the following is not advisable in the treatment of haemorrhagic shock?

- ☐ a. Supplementary oxygen should be given to maintain oxygen saturation at >95%
- ☐ b. Administer an initial, warmed fluid bolus of 6% hydroxyethyl starch. The usual initial dose is 1 L for adults
- ☐ c. Early administration of blood products at a low ratio of packed red blood cells to plasma and platelets can prevent the development of coagulopathy and thrombocytopenia
- ☐ d. Definitive control of haemorrhage and restoration of adequate circulating volume
- ☐ e. Insertion of a nasogastric tube

63. Which of the following is true?

- ☐ a. The sodium content of sweat is similar to that of plasma
- ☐ b. High volume nasogastric aspirates can lead to a hyperkalaemic acidosis
- ☐ c. The potassium concentration in small intestinal secretions is 5-10 mmol/L
- ☐ d. Pancreatic juice has a bicarbonate concentration of 80-100 mmol/L
- ☐ e. The sodium concentration in bile is half than in plasma

64. Which of the following is a risk factor for salt and water depletion in the older adult?

- ☐ a. Living alone and social deprivation
- ☐ b. Liver disease
- ☐ c. Obesity
- ☐ d. Congestive cardiac failure
- ☐ e. Cold weather

65. Which of the following medications can cause hyperkalaemia in the elderly?

- ☐ a. Frusemide
- ☐ b. Thiazide diuretics
- ☐ c. Salbutamol
- ☐ d. Angiotensin converting enzyme inhibitors
- ☐ e. Senna

66. Which of the following is true regarding free water?

- ☐ a. Most of the free water in the postoperative period is provided by intravenous administration of 0.9% saline
- ☐ b. 5% dextrose does not provide any free water
- ☐ c. Most of the free water in the postoperative period is provided by intravenous administration of Hartmann's solution
- ☐ d. Free water clearance is greater in response to hypertonic fluid administration than to hypotonic fluid administration
- ☐ e. Free water clearance is defined as the volume of plasma that is cleared of solute-free water per unit time

67. Which of the following is not true about estimated glomerular filtration rate?

- ☐ a. It is a mathematically derived value
- ☐ b. It is based on the serum creatinine concentration, age, sex and race
- ☐ c. It can also be calculated based on the blood urea concentration, age, sex and race
- ☐ d. It is expressed in ml/min/1.73m^2
- ☐ e. The eGFR value approximates to the percentage of kidney function

68. Which is not true about the passive leg raising test?

- ☐ a. It is best undertaken by lying the patient flat and passively raising their legs to 15°
- ☐ b. It is a bedside method to assess likely response to fluid administration

☐ c. If the patient develops dyspnoea, it indicates that the patient may be fluid overloaded
☐ d. Signs of haemodynamic improvement (e.g. rise in blood pressure, decrease in tachycardia, improved peripheral perfusion) at 30–90 seconds suggest an intravascular volume deficit likely to respond to intravenous fluids
☐ e. It may be undertaken with the patient initially semi-recumbent and then tilting the entire bed through 45°

69. Which of the following blood laboratory values is not in the normal range?
☐ a. Bicarbonate 24-32 mmol/L
☐ b. Magnesium 0.8-1.2 mmol/L
☐ c. Lactate 0.6-1.8 mmol/L
☐ d. Chloride 95-105 mmol/L
☐ e. Ionised calcium 2.2-2.6 mmol/lL

70. If you had to administer 2 litres of fluid over 24 hours, what rate would you set the infusion pump at?
☐ a. 100 ml/h
☐ b. 83 ml/h
☐ c. 110 ml/h
☐ d. 90 ml/h
☐ e. 60 ml/h

71. Which of the following medicines is not normally metabolised and/or excreted by the kidneys
☐ a. Penicillins
☐ b. Cehpalosporins
☐ c. Vancomycin
☐ d. Fractionated heparin
☐ e. Clindamycin

72. Clinical features of chronic kidney disease include all of the following except:
☐ a. Polycythaemia
☐ b. Restless legs
☐ c. Bone pain
☐ d. Muscle weakness
☐ e. Prutitus

73. Patients scheduled for elective surgery should be
☐ a. Starved for 12 hours before the induction of anaesthesia
☐ b. Starved for 8 hours before the induction of anaesthesia
☐ c. Allowed to eat for up to 4 hours and drink clear liquids for up to 1 hour before the induction of anaesthesia
☐ d. Starved for 24 hours before the induction of anaesthesia
☐ e. Allowed to eat for up to 6 hours and drink clear liquids for up to 2 hours before the induction of anaesthesia

74. Salt and water overload after gastrointestinal surgery can lead to

- ☐ a. Increased mesenteric blood flow
- ☐ b. Anastomotic dehiscence due to impaired wound healing
- ☐ c. Improved venous return
- ☐ d. Increased intestinal contractility
- ☐ e. Intestinal intramucosal alkalosis

75. The aims of postoperative fluid therapy include all of the following except:

- ☐ a. Avoidance of excessive fluid administration
- ☐ b. Achieving a state of as near zero fluid balance as possible
- ☐ c. Early resumption of oral fluids and diet
- ☐ d. Providing parenteral or enteral nutrition for the first five to seven days
- ☐ e. Supplementing patients with intravenous fluids if oral intake is inadequate

ANSWERS TO MULTIPLE CHOICE QUESTIONS

1-d, 2-d, 3-c, 4-a, 5-e, 6-b, 7-b, 8-c, 9-a, 10-d, 11-e, 12-a, 13-b, 14-c, 15-a, 16-b, 17-b, 18-c, 19-c, 20-a, 21-e, 22-a, 23-b, 24-c, 25-e, 26-d, 27-b, 28-d, 29-e, 30-d, 31-e, 32-e, 33-a, 34-d, 35-e, 36-e, 37-c, 38-e, 39-c, 40-a, 41-a, 42-b, 43-a, 44-d, 45-c, 46-c, 47-e, 48-c, 49-a, 50-d, 51-d, 52-a, 53-e, 54-b, 55-a, 56-b, 57-b, 58-c, 59-b, 60-e, 61-c, 62-b, 63-c, 64-a, 65-d, 66-e, 67-c, 68-a, 69-e, 70-b, 71-e, 72-a, 73-e, 74-b, 75-d

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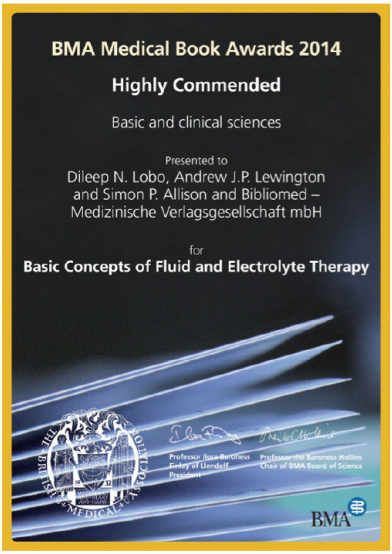
Reviews of the First Edition



"This is certainly a very helpful book, particularly for the junior staff who will be setting out in making decisions about the fluid balance of their patients in the preoperative period of patients or in particular disease states. In a way the junior staff should have this book at hand at all times. The strength of the book is that it is written in a very straightforward manner giving the basic outlines of how decisions on fluid resuscitation should be made and the thought process that underlie the decisions.

The book is really a handbook for practical guidance and in this regard it fulfils its purpose. As a source book it could be very helpful."

BMA Medical Book of the Year Awards Shortlist 2014

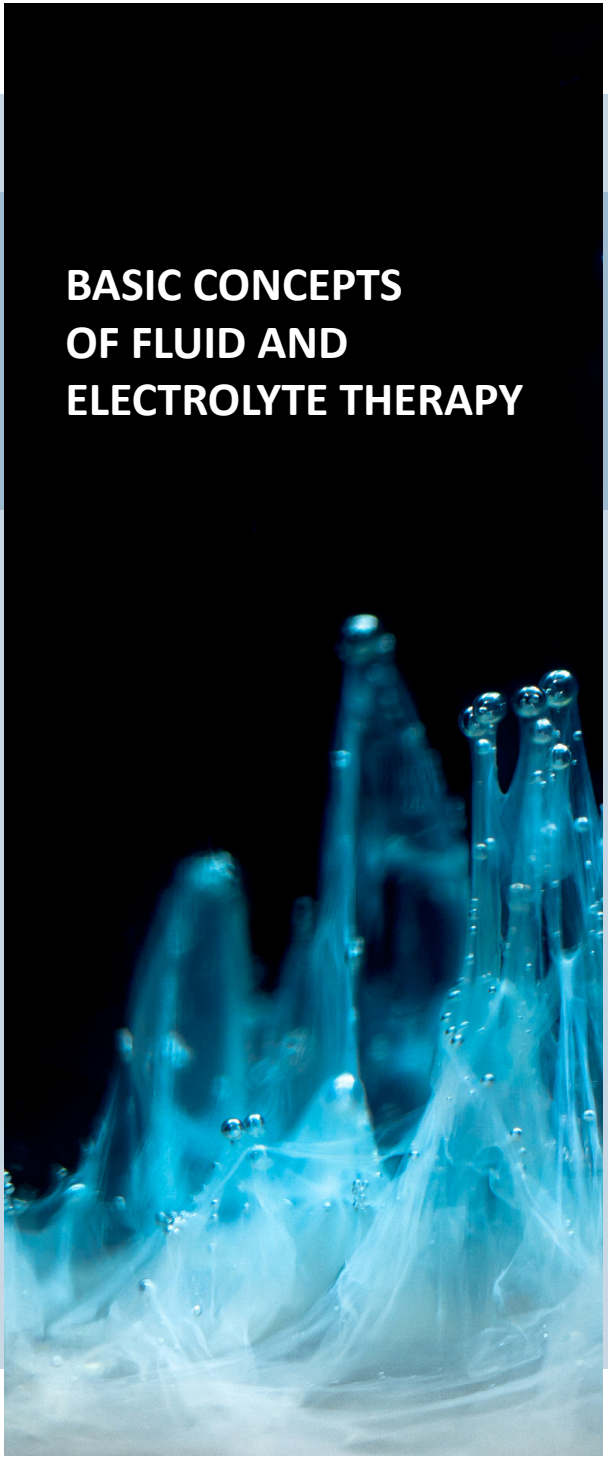
"Every junior doctor has been daunted at some point by the task of fluid prescription. Indeed, the evidence (both historical and more recent) also points toward educational deficits in this area. The book Basic Concepts of Fluid and Electrolyte Therapy does an excellent job of helping to demystify this process. The book provides a handy reference guide to everyday matters involving fluid prescription and electrolyte management.

Overall, this book is concise (but clinically adequate). I would highly recommend it to both medical students and junior doctors as a great 'real-world' introduction to fluid and electrolyte management. The book could easily form the basis of many case-based teaching scenarios for ward-based student attachments. Moreover, even the more experienced physician with limited time for a cover-to-cover read would undoubtedly find it a worthy reference in times of clinical quandary."

Angela King, Clinical Medicine 2013; 13: 524.

Dileep N. Lobo
Andrew J. P. Lewington
Simon P. Allison

BASIC CONCEPTS OF FLUID AND ELECTROLYTE THERAPY



2nd Edition