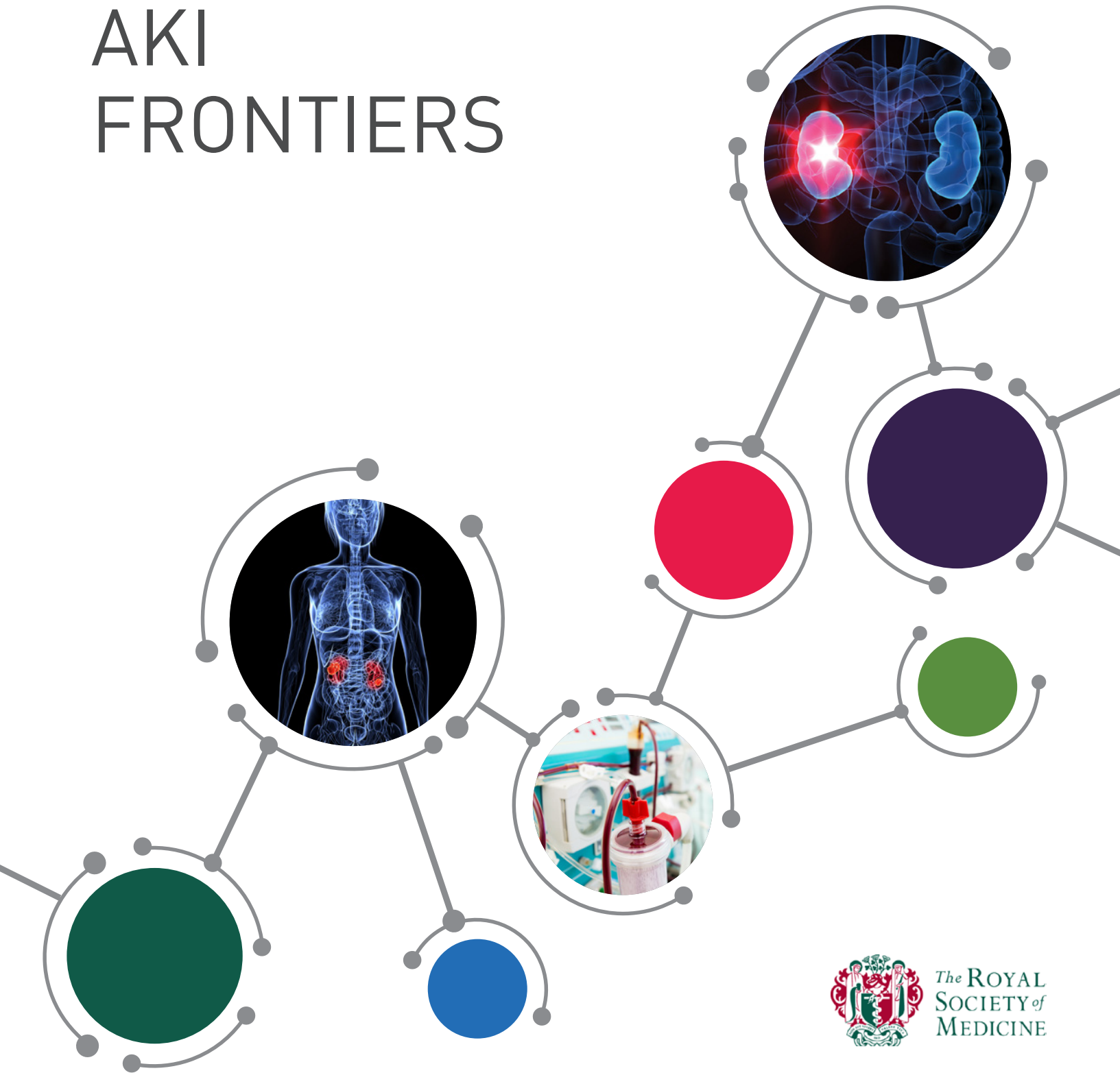


AKI FRONTIERS



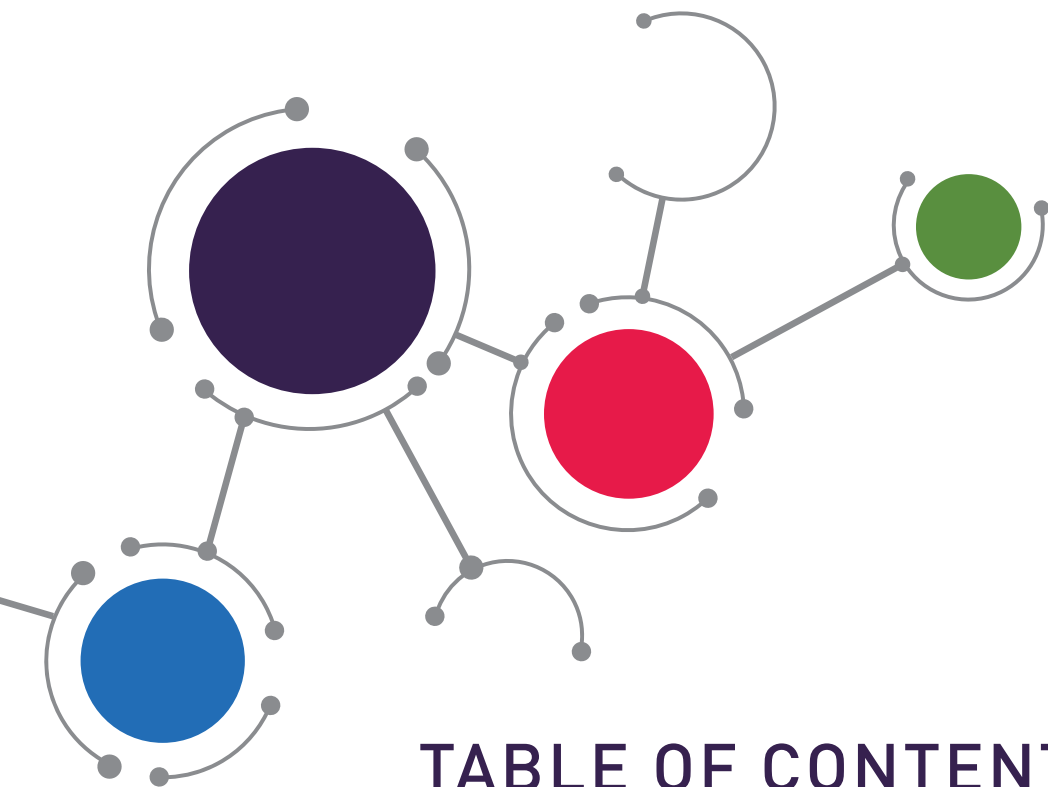


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INTRODUCTION TO AKI FRONTIERS

The AKI Frontiers conference will bring together investigators and experts in acute kidney injury from across the globe to discuss ongoing research into many different aspects of acute kidney injury. The UK Kidney Research Consortium AKI Clinical Study Group and London AKI Network continue to develop ways to improve outcomes for patients with AKI including research and education. The following chapters were selected because they focus on causes and management of AKI which were highlighted in the AKI frontiers conference and give practical information about how to approach patients with newly diagnosed AKI.

We hope you will enjoy reading these taster chapters as much as we have.

Dr Chris Laing,

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SUMMARY

Acute kidney injury (AKI) is a common complication of hospitalised patients with one million patients diagnosed annually in the United States alone. Chapter 1 "*Acute Renal Dysfunction*" from **Acute Care Surgery and Trauma: Evidence-Based Practice** examines which patients are at the greatest risk of AKI, the diagnostic tests available to determine subtype and severity of AKI, and the potential treatment strategies.

Fluid management of patients with AKI is of the utmost importance. Chapter 2 "*Acute Kidney Injury*" from **Making Sense of Fluids and Electrolytes: A Hands-on Guide** provides succinct guidance from initial investigation and assessment to special considerations in order to achieve optimal fluid management in AKI patients.

Disorders of acid-base homeostasis are common in patients with AKI, Chapter 3 "*Acid-Base Disturbances*" from **Emergency Medicine: Diagnosis and Management**, outlines the interpretation of arterial blood gas analysis for the diagnosis and subsequent management of acid-base disturbances.

Electrolyte disorders are also common in patients with AKI and are associated with cardiovascular emergencies, cardiac arrhythmias and cardiopulmonary arrest. Chapter 4 "*Electrolyte Disorders*" from **Emergency Medicine: Diagnosis and Management** details how to promptly recognise and treat potassium, sodium, calcium, and magnesium imbalances.



INTRODUCTION TO AKI FRONTIERS

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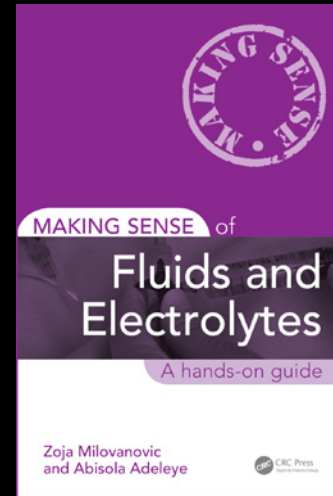
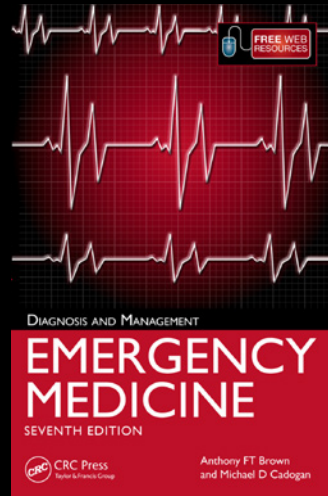
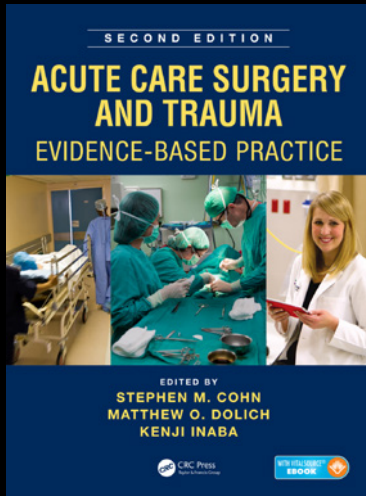
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Note to readers: References from the original chapters have not been included in this text. For a fully-referenced version of each chapter, including footnotes, bibliographies, references and endnotes, please see the published title. Links to purchase each specific title can be found on the first page of each chapter. As you read through this FreeBook you will notice that some excerpts reference previous chapter – please note that these are references to the original text and not the Freebook.

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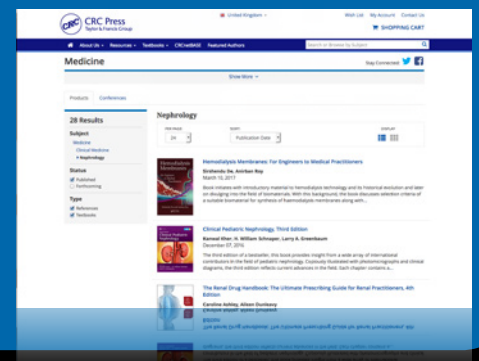
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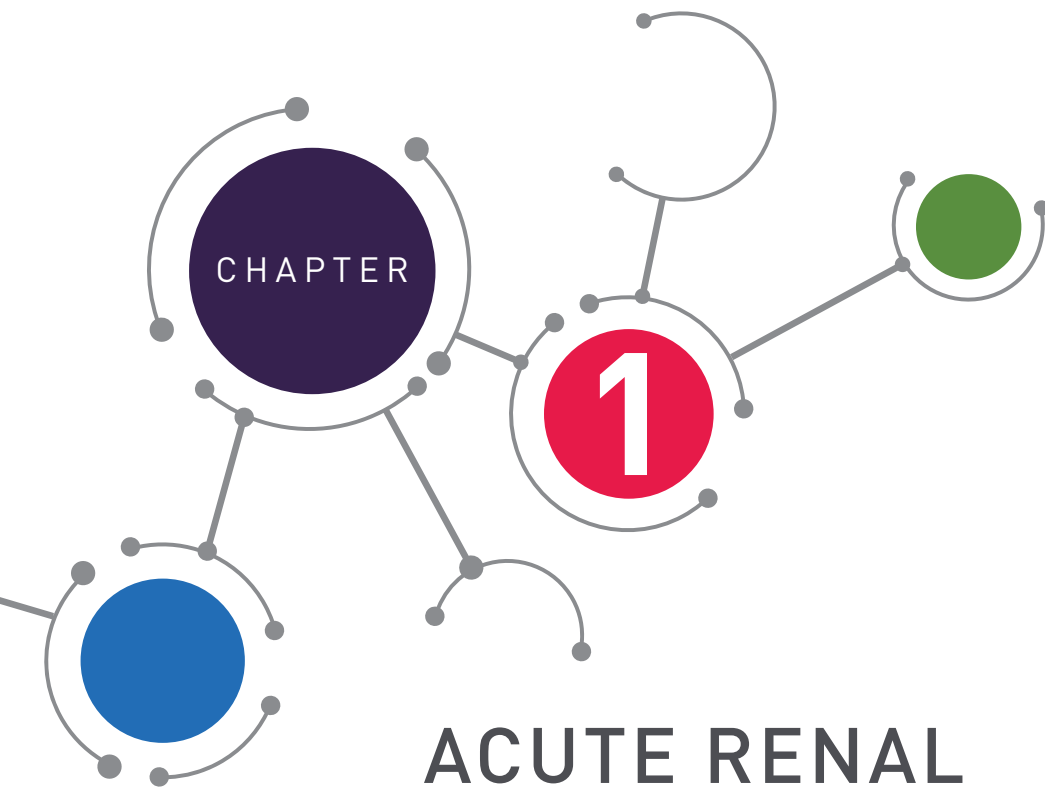


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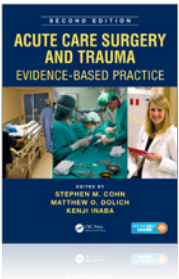




ACUTE RENAL DYSFUNCTION



1 :: ACUTE RENAL DYSFUNCTION



The following is excerpted from *Acute Care Surgery and Trauma: Evidence-Based Practice, 2nd Edition* by Stephen M. Cohn, Matthew O. Dolich and Kenji Inaba. ©2016 Taylor & Francis Group. All rights reserved.

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Acute renal dysfunction is a common complication of hospitalized patients that is associated with significant morbidity and mortality. Multiple classification systems have been developed, including risk, injury, failure, loss, end-stage renal disease (RIFLE), Acute Kidney Injury Network, and more recently, the Kidney Disease: Improving Global Outcomes (KDIGO). These classification systems are thought to identify acute kidney injury (AKI) and allow for severity grading based on changes in the level of serum creatinine (sCr) and urine output. However, there are significant limitations to the use of sCr. These limitations are highlighted by the recent discovery of serum and urinary biomarkers, as well as kidney-specific genes, expressed soon after kidney injury, which are changing that paradigm in which we view AKI. At present, there are multiple forms of kidney stress and damage that are known to raise sCr in hospitalized patients including prerenal, intrinsic renal, and postrenal causes. Sepsis, hypovolemia, chronic kidney disease, major trauma, and surgery all confer significantly increased risk of the most severe form of azotemia, called intrinsic AKI. Unfortunately, medical therapies to limit or reverse the intrinsic forms of AKI have thus far eluded researchers, and while the judicious use of fluids is appropriate in volume-depleted prerenal patients with renal failure, they may be dangerous in patients with renal failure of the edematous states such as heart failure. Neither the timing of renal replacement therapy nor its modality or intensity has been consistently shown to impact mortality or renal recovery. Intermittent hemodialysis is used for hemodynamically stable patients, whereas continuous renal replacement therapy is typically used for patients who are unstable or in shock. Peritoneal dialysis has fallen out of favor for the treatment of AKI, albeit a useful modality for chronic kidney disease.

INTRODUCTION

Acute renal dysfunction is a commonly encountered clinical entity with profound implications. In the United States, one million patients are diagnosed annually with acute renal dysfunction, and the incidence is rising. In its most severe form, called intrinsic acute kidney injury (AKI), acute renal dysfunction is a rapidly progressive disease that predicts morbidity and mortality. Patients with AKI often require admission to the intensive care unit (ICU), initiation of dialysis, and prolonged hospitalization. They encounter significant risk of both in-hospital death and the development of chronic kidney disease (CKD). Even small changes in serum creatinine (sCr) are associated with significant morbidity and mortality, underscoring the significance of this condition.



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In 2004, the Acute Dialysis Quality Initiative Group published a consensus definition known as the risk, injury, failure, loss, end-stage renal disease (RIFLE) classification system of AKI. This scheme identified three grades of AKI severity (risk, injury, and failure) based on relative changes in sCr and/or glomerular filtration rate (GFR) over a 7-day time period and/or absolute changes in urine output. There were also two AKI outcome classes (loss- and end-stage) determined by the duration of renal replacement therapy (RRT). From this definition, it is clear that the term “AKI” can encompass a spectrum of renal dysfunction: AKI does not represent only acute tubular necrosis (ATN) or acute hemodynamic stress; it encompasses both less severe alterations in kidney function, including the rapidly reversible physiologic changes typical of prerenal azotemia and slowly reversible tubular cell death. Despite its imprecision, the RIFLE criteria have been validated as an independent predictor of in-hospital mortality, with an increased risk of death found in all RIFLE grades, which increases with each subsequent grade. These criteria have established a degree of uniformity required for research on the prevention and treatment of AKI.

In 2007, the Acute Kidney Injury Network (AKIN) published their own diagnostic criteria based on relative changes in sCr within a 48 h time period and/or absolute changes in urine output. However, the AKIN criteria do not include GFR. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) classification was established as a hybrid of the RIFLE and AKIN classifications using both absolute changes of the sCr (≥ 0.3 mg/dL) within a 48 h time period, and relative changes ($\geq 50\%$ from baseline) within 7 days. It also included urine output in the criteria. In each of these classification systems, hospital mortality has been shown to increase in accordance with staging. However, in a retrospective observational study, Fujii et al. found that the RIFLE and KDIGO classification systems had a superior predictive ability for hospital mortality.

Despite the development of multiple new classification schemes for AKI, the reliance on the sCr as a marker of kidney damage has limited their ability to accurately distinguish structural kidney damage from reversible prerenal stress. More sensitive and specific biomarkers are needed to better identify patients with reversible causes of AKI from those with more severe etiologies.

RISK FACTORS

WHO IS AT RISK FOR AKI?

A combination of vascular, tubular, and inflammatory factors is known to be responsible for renal injury in most cases of AKI. Several cohort studies have attempted to define risk



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factors for the development of AKI. Among critically ill patients, sepsis is the most common condition associated with AKI. Bagshaw et al. found that AKI occurred in 42% of septic patients admitted to ICUs. In a prospective cohort study, Uchino et al. studied 30,000 patients admitted to 54 ICUs and found that sepsis contributed to 47% of cases of AKI. Additionally, many of the patients who develop AKI have a history of CKD. This finding is supported by data from Hsu et al., who reported that CKD is a risk factor for AKI that is severe enough to require RRT during hospitalization. CKD limits renal reserve during stress, and this may contribute to the elevated rates of AKI seen in patients with baseline renal dysfunction. Diminished renal reserve during stress also appears to place older patients at risk for severe AKI. Retrospective reviews of both public and private health delivery systems data in the United States demonstrate that older patients have an elevated rate of AKI compared to younger patients.

Hypovolemia is also a risk factor for renal ischemia and thus AKI. Reduced effective intravascular volume (i.e., from cirrhosis or congestive heart failure), which causes renal vasoconstriction and ischemia, also predisposes to AKI from further insults, such as contrast or nephrotoxins.

Perioperative AKI is associated with distinct set of risk factors. Preexisting conditions such as diabetes, CKD, cardiac disease, and advanced age increase the risk of perioperative AKI. Surgical procedures that produce higher rates of AKI include cardiac surgery requiring cardiopulmonary bypass, major intraabdominal surgery, vascular surgery requiring aortic manipulation, and/or cross-clamping and organ transplantation. Trauma patients are also at risk for AKI, particularly those with rhabdomyolysis. In a review of 436 consecutive admissions to a Level 1 trauma center, Gomes et al. found that 50% patients satisfied the RIFLE criteria, and that patients with higher severity trauma scores were more likely to develop in AKI.

Recommendation: Acute kidney injury (AKI) occurs in numerous clinical settings and, therefore, has a variety of risk factors. Conditions that confer significant risk of AKI include sepsis, baseline CKD, advanced age, hypovolemia, major surgery, and trauma (Grade B recommendation).

DIAGNOSIS

WHAT IS THE OPTIMAL DIAGNOSTIC TEST TO ESTABLISH AKI?

Despite its prevalence, the timely and early recognition of AKI remains difficult due to the inadequacies of sCr to definitively identify AKI. RIFLE, AKIN, and KDIGO criteria



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require an increase in sCr from baseline. This creates several problems: (1) baseline sCr may be unknown; (2) sCr is a delayed marker and, therefore, significant time may elapse after an injury until sCr reaches a diagnostic threshold; (3) the level of sCr may not accurately reflect the degree of renal injury since the kinetics of sCr are influenced by age, gender, muscle mass, nutritional status, hemodynamics, fluid status, and medications. These limitations have generated intense interest in the identification of sensitive and specific biomarkers that allow for the early diagnosis of AKI.

In recent years, a number of urinary proteins have been shown to be associated with AKI. These proteins are normally present at low concentration in the urine, but stressors activate their expression in different cells of the kidney, resulting in an increase in their urinary concentrations. The hope is that these proteins may serve as sCr-independent “biomarkers,” providing prospective data on the effects of toxic stimulation of the kidney.

These biomarkers include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), interleukin-18 (IL-18), liver fatty acid-binding protein (L-FABP), and cystatin C. Multiple studies have shown the promise of these biomarkers in identifying patients with AKI, and in predicting postoperative AKI. NGAL has been studied in over 16, patients including patients in the emergency room where it has been shown to be predictive of AKI and adverse clinical outcomes. NGAL is significantly elevated in intrinsic AKI, but NGAL is not elevated in rapidly reversible prerenal stress in humans or mice.

More recently, Kashani et al. found that urine insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2) both individually and in combination ($[TIMP-2] \times [IGFBP7]$) were more predictive of moderate to severe AKI within 12 h than other biomarkers, including urine or plasma NGAL, plasma cystatin C, urine KIM-1, urine IL-18, and urine L-FABP. Meersch et al. found that in addition to a rise in urinary $[TIMP-2] \times [IGFBP7]$ that is predictive of AKI within 4 h of cardiac surgery, a decline in its levels were predictive of renal recovery from AKI after cardiac surgery. However, these results need to be further validated in larger studies. Additionally, these genes are expressed predominately in glomeruli (<http://www.gudmap.org>; <http://www.proteinatlas.org>), and are also found in normal urine.

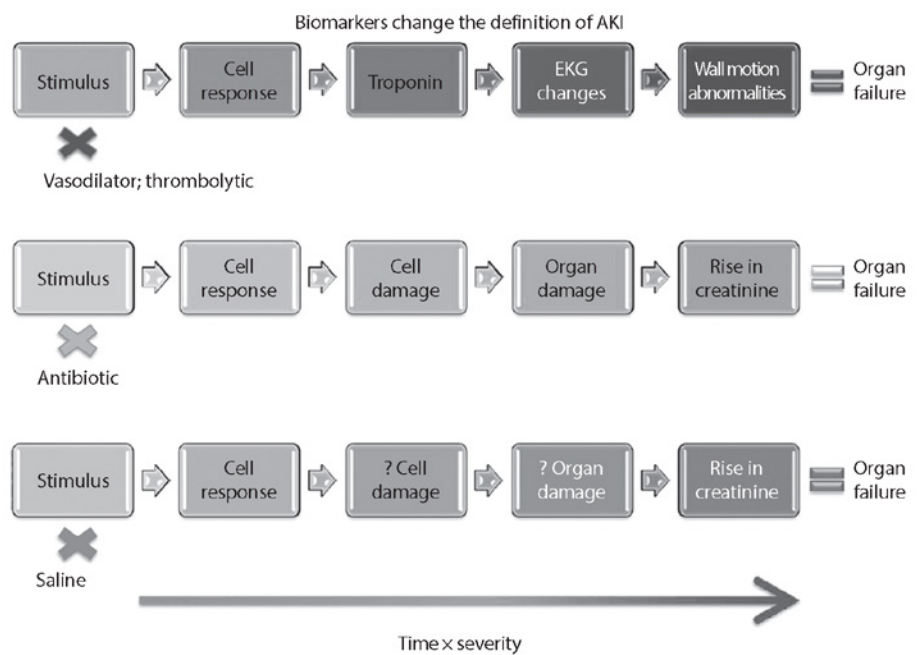
It is important to note that biomarkers are a relatively new concept in the field of nephrology. Validation of these biomarkers necessitates comparison to sCr, and this comparison has intrinsic difficulties given that sCr is an imperfect marker of AKI. As noted in **Figure 1.1**, cellular stress, cellular damage, organ damage, and organ failure form a pathway of increasing severity that has been well studied with



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Figure 1.1

Progressivity and severity of AKI. AKI starts with an injurious stimulus (e.g., sepsis, ischemia, and volume depletion) that activates a biological pathway that includes cellular responses, cellular damage, organ damage, and organ failure. Biomarkers such as troponin and NGAL activate long before and at lower severity of damage than measures of organ failure such as sCr. Many stimuli can activate sCr, but each may activate a distinct biological pathway (e.g., sepsis, shown in the middle panel compared with volume depletion shown in the bottom panel) and deserve a different treatment (antibiotics versus saline).



cardiology, but is a new paradigm within the field of nephrology. In the former case, the appearance of troponin defines a myocardial infarction, while the presence of troponin in addition to EKG changes and subsequently echocardiographic changes represents an ascending scale of severity of tissue damage. In AKI, only sCr has been recognized as a marker of kidney distress (Figure 1.1). Within this new paradigm of AKI, biomarkers that are upregulated in response to a weak stimulus without elevation of sCr indicate an earlier or less severe level of renal injury. Conversely, a strong stimulus will activate both the biomarkers and sCr, indicating a more severe injury. The utilization of biomarkers will allow for the identification of renal injury in the absence of overt renal failure.

Answer: While standardized creatinine-based definitions of AKI now exist, novel biomarkers hold great promise for expedient and accurate diagnosis (Grade B



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recommendation).

WHAT IS THE BEST APPROACH TO THE DIFFERENTIAL DIAGNOSIS OF AKI?

AKI is classically divided into three large categories: prerenal, intrinsic renal, and postrenal causes (Table 1.1).

Postrenal causes refer to any obstruction of urinary flow. This may be partial or complete, unilateral or bilateral, and may occur at any location from the renal pelvis to the urethra. Common causes of urinary obstruction include bladder outlet obstruction from benign prostatic hypertrophy, which may be exacerbated by the use of narcotic analgesics or anti-cholinergic medications in the hospital; a high index of suspicion for obstruction is necessary in any older man with unexplained AKI. Severe cystitis or obstruction of a Foley catheter may cause bladder outlet obstruction. An obstructing kidney stone may cause AKI in patients with single functioning kidney or baseline CKD. Obstruction can be evaluated by renal ultrasonography demonstrating hydroureter or hydronephrosis; however, it should be noted that in patients with early obstruction, significant volume depletion, or retroperitoneal fibrosis, normal ultrasound findings are expected despite urinary tract obstruction. Moreover, normal urine output does not exclude partial urinary tract obstruction, nor do normal creatinine values (e.g., unilateral kidney obstruction), and, in fact, are likely to delay the diagnosis.

Table 1.1

Differential Diagnosis of Acute Kidney Injury		
Prerenal + Related Syndromes	Intrinsic	Postrenal
Volume depletion	Ischemic acute tubular necrosis	Benign prostatic hyperplasia
Cirrhosis	Contrast nephropathy	Obstructed foley catheter
Congestive heart failure	Rhabdomyolysis	Hematuria with large clots
Third-spacing	Nephrotoxic acute tubular necrosis	UTI with bladder outlet obstruction
	Tumor lysis syndrome	Bilateral ureteral obstruction from:
	Acute interstitial nephritis	<ul style="list-style-type: none"> • Kidney stones • Tumor compression • Retroperitoneal fibrosis
	Malignant hypertension	
	Cholesterol emboli	
	Glomerulonephritis	
	<ul style="list-style-type: none"> • Lupus • Post-infectious • Anti-GBM • ANCA vasculitis • Cryoglobulinemia 	



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Distinguishing prerenal kidney stress from intrinsic AKI is more difficult, but necessary, given the significant increase in morbidity and mortality in the latter. Prerenal causes include volume depletion from dehydration, blood loss, and diuretics. Prerenal AKI can also result from volume overloaded or edematous states including congestive heart failure or cirrhosis, in which the total body fluid is increased, but the effective circulating volume is decreased due to movement of fluids from the intravascular into the extravascular space, causing decreased renal blood flow. Urinary studies can be helpful in distinguish prerenal from intrinsic renal causes. Prerenal causes are associated with low urine sodium (i.e., <20 mEq/L) and low fractional excretion of sodium $<1\%$, indicating intact sodium retention. However, several factors can decrease the diagnostic utility of urine sodium, including recently administered diuretics, CKD, and acute rehydration therapy. A blood urea nitrogen (BUN) to creatinine ratio of greater than 20:1 is also suggestive of prerenal azotemia; however, this is neither sensitive nor specific. Sepsis, high-protein enteral feeding, corticosteroid use, and upper gastrointestinal bleeding can all elevate BUN out of proportion to the creatinine and, conversely, liver disease and poor nutritional status will depress the BUN. Therefore, prerenal disease cannot be excluded by a normal BUN/creatinine ratio. It is important to note that fluid management cannot be determined based on serum or urinary findings alone, but must incorporate history and physical examination findings, since both volume depletion and congestive heart failure are “prerenal” causes of AKI, yet are managed very differently: IV fluids in the former group and IV diuresis and possible inotropic support in the latter group.

Urinary biomarkers are currently under investigation to determine if they can distinguish intrinsic renal failure from prerenal causes. Certain biomarkers, such as NGAL, are upregulated in response to tubular damage rather than quickly reversible prerenal azotemia, and, therefore, high urinary levels are expected in intrinsic renal failure but not prerenal azotemia. Genetic studies are now ongoing to identify novel biomarkers in the kidney. Ongoing studies have demonstrated that gene expression differs in subjects with different types of AKI, even when sCr levels are equivalent. Many genetic pathways are activated in ischemia, while fewer genes are activated in prerenal azotemia, with only a small degree of overlap between the two conditions. This suggests that there should be distinct molecular identifications to each state.

Recommendation: When evaluating AKI, a systematic approach that includes prerenal, intrinsic renal, and postrenal causes is critical as therapy is substantially different between these groups. Urinary studies can help distinguish prerenal AKI from intrinsic AKI. Urinary biomarkers, including NGAL, have been repeatedly shown to separate subsets of AKI (Grade B recommendation).



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WHAT ARE COMMON CAUSES OF INTRINSIC AKI SEEN ON SURGICAL SERVICES

Causes of intrinsic renal failure commonly encountered on surgical services include ischemic and nephrotoxic ATN, contrast-induced nephropathy (CIN), and allergic interstitial nephritis. Postoperative AKI may occur to up to 25% of patients undergoing coronary artery bypass grafting. Medications including vancomycin and aminoglycosides are an important cause of nephrotoxic ATN. Betalactam and sulfonamide antibiotics, flouroquinolones, proton pump inhibitors, and non-steroidal anti-inflammatory drugs (NSAIDs) are associated with acute interstitial nephritis. The clinical scenario is important in diagnosing acute interstitial nephritis as these patients may have other allergic symptoms including rash, fever, and peripheral eosinophilia. NSAIDs, such as ketorolac and ibuprofen, can also cause ischemic ATN, and should be used with caution in elderly patients and avoided entirely in patients with CKD or cardiac disease.

CIN typically occurs in patients with other underlying risk factors including hypotension, use of an intraaortic balloon pump, congestive heart failure, older age, anemia, diabetes, high contrast volumes, and elevated sCr or low GFR. Using a score model developed for patients undergoing percutaneous coronary intervention, the risk of CIN ranges from 7.5% for low-risk patients to $\geq 57.3\%$ for the patients at the highest risk; findings have been validated in other studies. Strategies for preventing CIN include discontinuing furosemide and angiotensin-converting enzyme inhibitors or angiotensin receptor blocking medications prior to contrast exposure. Patients should be hydrated with either normal saline or sodium bicarbonate at a rate of 1 mL/kg/h for 12 h prior to contrast and 12 h after contrast exposure. If a patient is known to have congestive heart failure, then the rate of IV fluid administration should be decreased to 0.5 mL/kg/h. Once CIN is established and urine output has decreased, it is wise to stop standing IV fluids to prevent worsening volume overload.

Pigment-induced nephropathy, due to either rhabdomyolysis (myoglobin pigment) or massive hemolysis (hemoglobin pigment), results from direct tubular damage from these substances. Prophylaxis with judicious IV fluids are recommended to prevent AKI in patients with rhabdomyolysis or hemolysis.

MANAGEMENT

DOES TIME OF RRT INITIATION, MODALITY, OR INTENSITY IMPACT MORTALITY?

RRT is the definitive treatment for complications of AKI (extracellular fluid volume overload, solute imbalance, and uremia) that are intractable to medical management.



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Nevertheless, the current literature offers incomplete guidance as to the optimal timing, method, and intensity of such therapy. While case-control and retrospective studies suggested “early” dialysis reduces mortality, two randomized clinical trials produced conflicting results. In 2002, a trial of 106 patients initiated “early” dialysis if urine output was less than 30 mL/h after 6 h but did not find a difference with regard to mortality or recovery of renal function in survivors. A 2004 trial found a large reduction in mortality with early dialysis, defined by postoperative urine output (RR = 0.17; 95% CI = 0.05–0.61), but weak methods and a small sample size ($N = 28$) temper this conclusion. The lone observational study in this area found that the risk of death in critically ill AKI patients was significantly decreased by initiating RRT before levels of BUN were greater than 76 mg/dL (adjusted hazard ratio = 0.54; 95% CI = 0.34–0.86). Based on this evidence, a 2008 systematic review of adult patients concluded that the available literature does not permit a definitive statement as to the optimal timing of acute RRT initiation. However, the pediatric literature suggests that there may at least be a mortality benefit to treating patients with RRT before they become significantly volume-overloaded. This fits with a model developed by Goldstein for patients with AKI in which there are three phases to fluid management: (1) fluid resuscitation/repletion, (2) fluid balance maintenance, and (3) fluid removal/recovery. This model requires clinicians to diligently monitor patients’ volume status.

Debate also persists regarding the preferred mode of dialysis. Available methods include intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT), with significant differences between these two techniques. IHD is conventionally performed three times a week in 4 h sessions via venovenous access. Because of more rapid fluid shifts, IHD requires hemodynamic stability. Conversely, CRRT is performed continuously using venovenous or arteriovenous access and reduced blood flow and ultrafiltration rates. In doing so, CRRT offers gradual solute and fluid clearance and, therefore, is the preferred choice in patients who are not hemodynamically stable. Despite the theoretical advantage of more “physiologic” restoration of solute and fluid balance, CRRT has not been found to offer a survival benefit compared with IHD. While methodological concerns, such as patient selection, plague this literature, no recent randomized control trial has demonstrated a mortality advantage to CRRT. Similarly, numerous meta-analyses have concluded that CRRT does not appear to confer a survival advantage over IHD. On the other hand, it is likely that sicker patients are offered CRRT, rather than IHD.

Six randomized trials have analyzed whether the dose of dialysate administered with CRRT impacts mortality. Two early studies produced preliminary evidence to suggest that increased CRRT intensity decreases mortality. Ronco et al. found that patients



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who received doses of 45 or 35 mL/kg/h demonstrated reduced mortality compared to patients who received doses of 20 mL/kg/h (RR = 0.72; 95% CI = 0.54–0.94 and RR = 0.73; 95% CI = 0.56–0.96, respectively). However, the preponderance of subsequent evidence has come to suggest that CRRT dose does not affect mortality. In 2002, Bouman et al. found no decrease in mortality among 106 patients who sustained higher hemofiltration volumes compared to lower volumes (48 versus 20 mL/kg/h). Similarly, Tolwani et al. found no difference in mortality between 200 patients randomized to receive CRRT dose of 35 or 20 mL/kg/h. In a multicenter 1100 patient randomized trial, Palevsky et al. did not note a mortality difference between patients receiving CRRT dose of 35 versus 20 mL/kg/h. Bellomo et al. conducted a 1500 patient trial and found no mortality difference at 90 days between patients who received a dose of 40 mL/kg/h and those who received 25 mL/kg/h. In addition, none of these studies reported a difference in rates of recovery of renal function following a more intense CRRT treatment. Given this body of evidence, most authors recommend achieving flow rates of 20 mL/kg/h. Higher rates may be used in cases with clinically significant metabolic acidosis or hyperkalemia or severe catabolic disease.

Early studies implied that more frequent IHD might also reduce mortality among critically ill patients with AKI. Schiffel et al. studied 160 patients and found reduced mortality among patients treated with daily IHD as compared to an alternating day schedule. Another group found reduced mortality among 34 patients randomized to receive either IHD to maintain BUN levels less than 60 mg/dL and sCr levels less than 5 mg/dL as compared to conventional IHD schedule. In spite of these early reports, a more recent, large randomized trial with 1100 patients failed to demonstrate a mortality benefit to daily IHD in AKI.

Recommendation: Neither the exact timing of RRT initiation, modality of dialysis, or intensity of the therapy above a minimum seem to impact mortality or renal recovery (Grade B recommendation).

WHAT ARE POTENTIAL PHARMACOLOGIC TREATMENTS OF AKI?

Initial therapy for suspected prerenal AKI secondary to volume depletion includes a judicious trial of fluid repletion in the appropriate clinical setting, unless evidence of congestive heart failure or pulmonary edema is present. Conversely, diuretics are useful in right-sided congestion that may cause congestive nephropathy, but more commonly diuretics are utilized in an attempt to improve urine output and manage volume overload in a patient with AKI. Nonetheless, numerous studies have found that diuretics do not decrease mortality or improve renal outcomes in established



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renal failure, albeit that both higher fluid balance and lower urine volumes were shown to be independently associated with 28-day mortality of AKI patients in one multicenter ICU study.

Various vasoactive substances have also been trialed in AKI. Low or renal-dose dopamine has been proposed to preferentially reduce renal vasoconstriction and thus advocated as a technique to ameliorate renal dysfunction. Several recent meta-analyses have not documented reduced mortality or improved renal function with low-dose dopamine and have explicitly argued against its use. Fenoldopam is a pure dopamine A-1 receptor agonist that increases blood flow to the renal cortex and outer medulla. Two meta-analyses, one in critically ill patients following cardiac surgery and one in critically ill patients with or at risk for AKI, found that fenoldopam reduced the need for renal replacement therapy, decreased mortality, and reduced length of stay. Heterogeneity among the analyzed studies limited this conclusion, and when Bove et al. randomized postcardiac surgery patients to fenoldopam or placebo, there was no difference in the rate of renal replacement therapy or mortality, although those receiving fenoldopam had a higher rate of hypotension. Atrial natriuretic peptide (ANP) is produced by modified cardiac myocytes and increases GFR through afferent arteriolar vasodilation and efferent arteriolar vasoconstriction. ANP has been mainly studied in the setting of postcardiac surgery AKI. While systematic reviews found a reduced need for RRT in AKI patients, other meta-analyses have concluded that the lack of high-quality studies limits this conclusion.

Another area of active research concerns the use of growth factors in the treatment of AKI. Noting that expression in animal models of insulin-like growth factor (IGF) decreased during ischemia and increased coincident with renal recovery, Hammerman et al. found that IGF administration ameliorated AKI in animal models. Translation of this concept from animals to humans has, however, proven difficult. Similarly, while large doses of erythropoietin improved AKI in animal models, a randomized, placebo-controlled trial of erythropoietin revealed that prophylactic administration did not decrease rates of AKI in the intensive care setting.

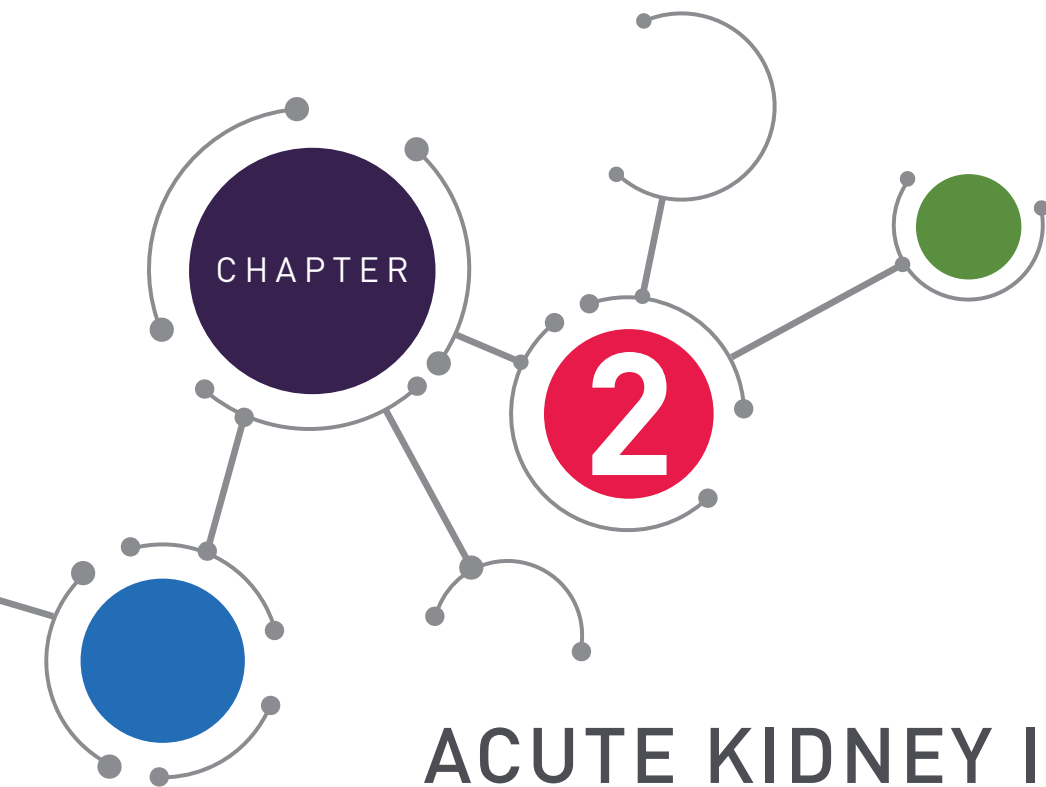
Recommendation: Medical therapies to limit or reverse AKI have thus far eluded researchers (Grade B recommendation).



1 :: ACUTE RENAL DYSFUNCTION

Table 1.2 • Clinical Questions Summary – Summarizes the clinical questions posed by practicing clinicians regarding AKI and assigns a grade based on the level of evidence.

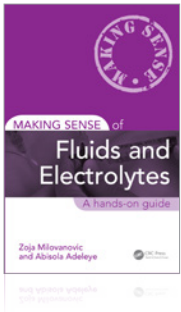
Question	Answer	Grade of Recommendation
Who is at risk for AKI?	Acute kidney injury (AKI) occurs in numerous clinical settings and therefore has a variety of risk factors. Conditions which confer significant risk of AKI include sepsis, baseline CKD, advanced age, hypovolemia, major surgery, and trauma.	B
What is the optimal diagnostic test to establish AKI?	While standardized creatinine-based definitions of AKI now exist, novel biomarkers hold great promise for expedient and accurate diagnosis.	B
What is the best approach to the differential diagnosis of AKI?	When evaluating AKI, a systematic approach that includes prerenal, intrinsic renal, and post-renal causes is critical as therapy is substantially different between these groups. Urinary studies can help distinguish pre-renal AKI from intrinsic AKI. Urinary biomarkers, including NGAL, have been repeatedly shown to separate subsets of AKI.	B
Does time of RRT initiation, modality, or intensity impact mortality?	Neither the exact timing of RRT initiation, nor modality of dialysis, nor intensity of the therapy above a minimum seem to impact mortality or renal recovery.	B
What are potential pharmacologic treatments of AKI?	Medical therapies to limit or reverse AKI have thus far eluded researchers.	B



ACUTE KIDNEY INJURY



2 :: ACUTE KIDNEY INJURY



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AKI is commonly seen in hospitalised patients. Essentially AKI encompasses acute renal deterioration of any cause.

HISTORY

CURRENT MEDICAL PROBLEM

There are many risk factors for AKI such as the following:

- Sepsis
- Liver failure
- Heart failure (HF)
- Diabetes mellitus
- Major surgery
- Trauma
- Old age and physical frailty
- Ischaemic heart disease (IHD)
- Nephrotoxic drugs

Broadly speaking, the causes for AKI can be divided into three groups, which are as follows:

- Pre-renal
- Renal
- Post-renal

Pre-renal AKI, which is the most commonly seen type, is caused by volume depletion. Renal AKI may be caused by drugs (such as angiotensin-converting enzyme [ACE]-inhibitors) or autoimmune conditions. Post-renal AKI is caused by obstruction. It is vital to identify the cause for the AKI early, as this dictates management. It is equally important to treat the underlying condition and stop any nephrotoxic drugs.

CURRENT FLUID STATUS

A thorough clinical assessment of the patient's volume status, is of utmost importance. Patients who are deemed volume-depleted require fluid resuscitation, patients who are deemed euvoelaemic do not necessarily require any IVF and patients who are clinically fluid-overloaded require loop diuretics or even emergency



2 :: ACUTE KIDNEY INJURY

haemofiltration in an HDU setting. The clinical aim is to achieve and maintain a euvolaemic state.

Patients with AKI can have a normal urine output (prognostically favourable), be polyuric (which tends to occur in the resolving stages of AKI) or be oligoanuric. The latter carries the worst prognosis and managing these patients is often quite challenging, because they require very frequent assessments of their fluid status. If they are clinically euvolaemic, a 'watch and wait' strategy often has to be adopted until the patient either improves or deteriorates.

INVESTIGATIONS

A urine dipstick offers useful information. If more than one plus of protein is detected, send off a urinary polymerase chain reaction (PCR) spot urine test. If a renal cause for the AKI is suspected, it is advisable to send a nephritic screen, complement levels, an auto-antibody screen and a myeloma screen in elderly patients. In this patient group, seek advice from a nephrologist early.

According to *NICE* Guideline 169, an urgent renal ultrasound (i.e. within 6 hours) should be performed in the following cases:

- Suspected renal obstruction
- Suspected pyonephrosis
- Patients with oligo-anuria
- Renal transplant patients

MANAGEMENT

TREAT THE UNDERLYING CAUSE

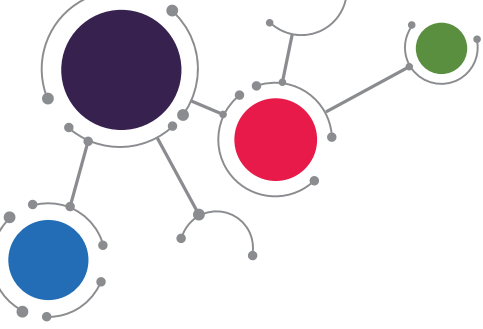
Specific management of each condition is required, which is beyond the scope of this book.

TREAT THE CURRENT FLUID STATUS

The KDIGO Guideline (2012) recommends a balanced crystalloid, such as Hartmann's or Plasmalyte, as the first-line fluid. Both fluids are alkalinising and have 'buffering' effects, which is desirable as most AKI patients frequently have a degree of metabolic acidosis and also often lose bicarbonate in the urine. Plasmalyte has the advantage that it contains less chloride than Hartmann's. There is some evidence that

REMEMBER!

If the cause of the AKI is thought to be pre-renal, patients do not necessarily require an ultrasound scan (USS) provided they are clinically improving.



2 :: ACUTE KIDNEY INJURY

hyperchloraemia is an independent predictor of mortality and leads to worse patient outcomes, which is why it should be avoided.

Normal saline contains a lot of chloride (154 mmol/L) and should ideally be avoided, unless the patient has severe hyperkalaemia.

1.26% sodium bicarbonate may be an appropriate fluid to administer in AKI patients who are fluid-depleted, have a metabolic acidosis with concomitant hyperkalaemia and a low intrinsic bicarbonate level on their blood gas. It is advisable to seek senior input in these cases.

Criteria for emergency renal replacement therapy are as follows:

- Symptomatic uraemia
- Fluid overload refractory to loop diuretics, glyceryl trinitrate (GTN), morphine and continuous positive airway pressure (CPAP)/Optiflow
- A persistent severe metabolic acidosis
- Refractory severe hyperkalaemia

REVIEW OF IMPLEMENTED TREATMENT

Patients with renal pathology will require regular review of their renal function via urine output and U+Es.

SPECIAL CONSIDERATIONS – FLUID MANAGEMENT IN PATIENTS WITH RENAL PATHOLOGY

FLUID THERAPY IN CHRONIC RENAL FAILURE

Clinical evaluation of volume status is vital in this patient group. Dialysis patients are usually on a fluid restriction regime and their management should always be discussed with their primary dialysis centre. The same rule applies to patients with a renal transplant. If there is clinical evidence of organ underperfusion, small aliquots of IVF may be appropriate. Balanced crystalloids should be the first-line choice. Monitor potassium and avoid hyperkalaemia.

RHABDOMYOLYSIS

Rhabdomyolysis leads to release of myoglobin from muscle tissue. Under certain conditions, for example in volume depletion and acidic urine, myoglobin can precipitate with the body's intrinsic Tamm-Horsfall protein in the renal tubules and



2 :: ACUTE KIDNEY INJURY

cause/exacerbate AKI. Early aggressive IVF therapy is the most important aspect of treatment and is required to 'flush the kidneys', increase estimated glomerular filtration rate (eGFR), minimise the nephrotoxic effects of myoglobin and aid its elimination from the body.

The treatment goal is to achieve 'high ins and outs', i.e. aggressive fluid therapy with a high urine output.

There is some evidence that urine alkalinisation may prevent precipitation of myoglobin and hence prevent AKI – pay particular attention to the urinary pH on a urine dipstick. If it is less than 6.50 (i.e. acidic), use intravenous 1.26% sodium bicarbonate to alkalinise the urine, aiming for a urinary pH of greater than 6.50. Maintain this therapy until the myoglobinuria has resolved (as evidenced by clear urine and a urine dipstick negative for blood).

Monitor the patient's U+Es, including calcium, as well as the creatine kinase (CK).

RADIOLOGICAL CONTRAST AND IV FLUIDS

Patients who require investigations involving iodinated contrast agents and who either have established AKI or are at risk of contrast-induced nephropathy (same risk factors as for AKI) should have renoprotective measures instituted prior to their investigation. Unless the patient is hypervolaemic, current evidence supports intravenous pre-hydration with normal saline or 1.26% sodium bicarbonate to ensure a euvolaemic state before any contrast is administered. There is also some weak evidence that oral N-acetylcysteine may help prevent contrast-induced nephropathy.

It is advisable to familiarise yourself with your hospital's trust policy and to inform the radiology department that a patient has or is at risk of AKI. Iso- or low-osmolar agents with lower iodine contents are often selected in these cases.

You should also consider temporarily stopping any nephrotoxic drugs, particularly if the patient has significantly impaired renal function or chronic renal failure with an eGFR of less than 60 mL/min/1.73 m².

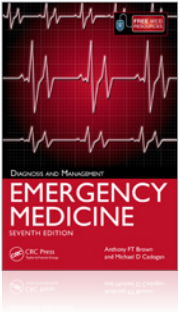
Post contrast exposure, the patient's renal function should be monitored for up to 5 days.



ACID-BASE DISTURBANCES



3 :: ACID-BASE DISTURBANCES



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ARTERIAL BLOOD GAS INTERPRETATION

Blood gas analysis provides information regarding potential primary and compensatory processes that affect the body's acid–base buffering system.

Acidosis is an abnormal process that increases the serum hydrogen ion concentration, lowers the pH, and results in acidaemia.

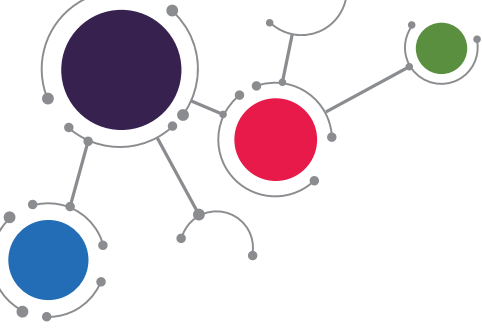
Alkalosis is an abnormal process with decrease in the hydrogen ion concentration, resulting in alkalaemia.

- 1 Blood gas analysis is used to:
 - (i) Determine the adequacy of oxygenation and ventilation.
 - (ii) Assess the respiratory function.
 - (iii) Determine the acid–base balance.
- 2 Interpret the arterial blood gas result in a stepwise manner as follows (see Table 3.1):
 - (i) Determine the adequacy of oxygenation (PaO_2):
 - (a) normal range 80–100 mmHg (10.6–13.3 kPa)
 - (b) provides direct evidence of hypoxaemia
 - (c) determine if there is a raised A-a gradient due to VQ mismatch/shunting, if there is a lower than expected PaO_2

Table 3.1 • Determining the likely acid–base disorder from the pH, PaCO_2 and HCO_3

pH	PaCO_2	HCO_2	Acid–base disorder
↓	N	↓	Primary metabolic acidosis
↓	↓	↓	Metabolic acidosis with respiratory compensation
↓	↑	N	Primary respiratory acidosis
↓	↑	↑	Respiratory acidosis with renal compensation
↓	↑	↓	Mixed metabolic and respiratory acidosis
↑	↓	N	Primary respiratory alkalosis
↑	↓	↓	Respiratory alkalosis with renal compensation
↑	N	↑	Primary metabolic alkalosis
↑	↑	↑	Metabolic alkalosis with respiratory compensation
↑	↓	↑	Mixed metabolic and respiratory alkalosis

Note: respiratory compensation occurs rapidly by changes in PaCO_2 . Renal compensation occurs more slowly by changes in HCO_3 .
N, normal.



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(d) assuming 100% humidity at sea level, the A-a gradient can be calculated by:

$$\begin{aligned} & - \text{A-a gradient} = P_A O_2 - P_a O_2 \\ & \text{where } P_A O_2 = (F_i O_2 \times (760 - 47)) - (P_a CO_2 / 0.8) \end{aligned}$$

(e) normal A-a gradient is <10 torr (mmHg), or approximately $< (\text{age}/4) + 4$.

(ii) Review the pH or hydrogen ion status:

(a) normal range pH 7.35–7.45 (H^+ 35–45 nmol/L)

(b) acidaemia is a pH <7.35 (H^+ >45 nmol/L)

(c) alkalaemia is a pH >7.45 (H^+ <35 nmol/L).

(iii) Determine the respiratory component ($PaCO_2$):

(a) normal range 35–45 mmHg (4.7–6.0 kPa)

(b) $PaCO_2 >45$ mmHg (6.0 kPa):

- acidaemia indicates a primary respiratory acidosis
- alkalaemia indicates respiratory compensation for a metabolic alkalosis

(c) $PaCO_2 <35$ mmHg (4.7 kPa):

- alkalaemia indicates a primary respiratory alkalosis
- acidaemia indicates respiratory compensation for a metabolic acidosis

(iv) Determine the metabolic component (bicarbonate, HCO_3^-):

(a) HCO_3^- normal range 22–26 mmol/L

(b) $HCO_3^- <22$ mmol/L:

- acidaemia indicates a primary metabolic acidosis
- alkalaemia indicates renal compensation for a respiratory alkalosis

(c) $HCO_3^- >26$ mmol/L:

- alkalaemia indicates a primary metabolic alkalosis
- acidaemia indicates renal compensation for a respiratory acidosis.

3 This approach will determine most primary acid–base disturbances and their associated renal or respiratory compensatory changes.

4 Remember:

(i) Renal or respiratory compensation is always a secondary process and should really not then be described in terms of an ‘acidosis’ or ‘alkalosis’:

(a) rather, in the presence of metabolic acidaemia, think of the respiratory compensation as ‘compensatory hyperventilation’ rather than a ‘secondary respiratory alkalosis’.

(ii) Chronic compensation returns the pH value towards normal, but overcompensation never occurs.



3 :: ACID-BASE DISTURBANCES

(iii) The presence of a normal pH with abnormal HCO_3^- and PaCO_2 suggests both a primary respiratory and a primary metabolic process are present:

(a) pH normal: $\text{PaCO}_2 > 45 \text{ mmHg}$ (6.0 kPa), $\text{HCO}_3^- > 26 \text{ mmol/L}$

- dual primary process involving a primary respiratory acidosis and a primary metabolic alkalosis

(b) pH normal: $\text{PaCO}_2 < 35 \text{ mmHg}$ (4.7 kPa), $\text{HCO}_3^- < 22 \text{ mmol/L}$

- dual primary process involving a primary respiratory alkalosis and a primary metabolic acidosis.

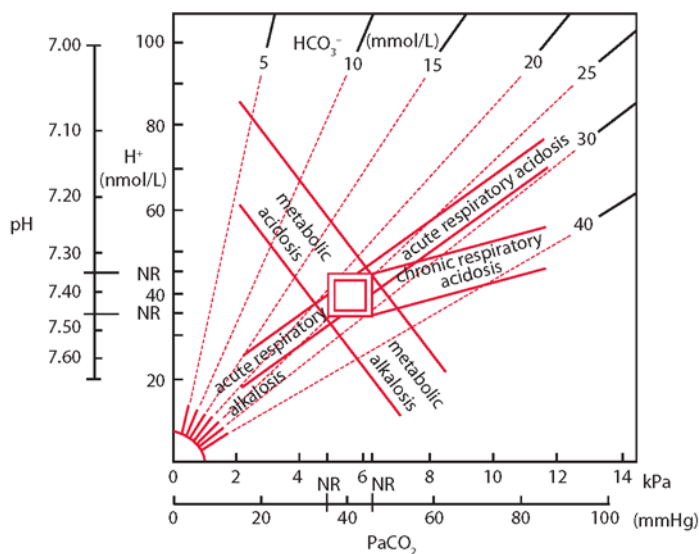
5 Alternatively, for simplicity, use an acid–base nomogram to plot and read off the interpretation of the arterial blood gas abnormality (see Figure 3.1)!

METABOLIC ACIDOSIS

DIAGNOSIS

- 1 An abnormal process or condition leading to the increase of fixed acids in the blood, best determined by a fall in plasma bicarbonate to less than 22 mmol/L.
- 2 Metabolic acidosis may be associated with a high, normal, or low anion gap.
 - (i) The anion gap is calculated from the equation $[\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])$ with all units in mmol/L.
 - (ii) A normal anion gap is 8–16.

Figure 3.1 • Acid–base nomogram for plotting interpretation of the arterial blood gas (NR is normal range)





3 :: ACID-BASE DISTURBANCES

- 3 Causes of a *high* anion gap metabolic acidosis (anion gap >16) include:
 - (i) Increased acid production:
 - (a) ketoacidosis, e.g. diabetes, alcoholism, starvation
 - (b) lactic acidosis (serum lactate >2.5 mmol/L):
 - type A: impaired tissue perfusion in cardiac arrest, shock, hypoxia, sepsis, mesenteric ischaemia
 - type B: impaired carbohydrate metabolism in hepatic or renal failure, lymphoma, pancreatitis and drugs such as metformin and salbutamol.
 - (ii) Decreased acid excretion, as in renal failure.
 - (iii) Exogenous acid ingestion:
 - (a) methanol, ethylene glycol, iron, cyanide and salicylates.
- 4 Causes of a *normal* anion gap metabolic acidosis (anion gap 8–16) include:
 - (i) Renal:
 - (a) renal tubular acidosis
 - (b) carbonic anhydrase inhibitors.
 - (ii) Gastrointestinal:
 - (a) severe diarrhoea
 - (b) small bowel fistula
 - (c) drainage of pancreatic or biliary secretions.
 - (iii) Other:
 - (a) rapid large volume sodium chloride infusion, ammonium chloride
 - (b) recovery from ketoacidosis.
- 5 The body compensates to reduce the acid load by hyperventilation. The expected compensatory reduction in PaCO₂ may be calculated (**see Table 3.2**):
 - (i) The acidosis is only partially compensated if the PaCO₂ value is higher than predicted.
 - (ii) A primary respiratory alkalosis coexists if the PaCO₂ value is lower than predicted.
- 6 There are few specific clinical features due to an acute metabolic acidosis itself, other than hyperventilation known as Kussmaul breathing.
- 7 Urea and electrolytes (U&Es) confirm a primary fall in plasma bicarbonate below 22 mmol/L and usually show an associated rise in plasma potassium from an extracellular shift.



3 :: ACID-BASE DISTURBANCES

Table 3.2 • Predicting the expected compensatory changes in PaCO₂ and HCO₃

	Metabolic acidosis		Metabolic alkalosis	
Predicted PaCO₂ (kPa)	0.2 × [HCO ₃] + 1 kPa (+/-0.25)		$\frac{[\text{HCO}_3]}{10} + 2.5 \text{ kPa (+/-0.7)}$	
Predicted PaCO₂ (mmHg)	1.5 × [HCO ₃] + 8 mmHg (+/-2)		0.7 × [HCO ₃] + 20 mmHg (+/-5)	
	Respiratory acidosis		Respiratory alkalosis	
Predicted HCO₃ (mmol/L) [PaCO₂ (kPa)]	Acute 24 + (PaCO ₂ - 5.33) × 0.75	Chronic 24 + (PaCO ₂ - 5.33) × 3	Acute 24 - (5.33 - PaCO ₂) × 1.5	Chronic 24 - (5.33 - PaCO ₂) × 3.75
Predicted HCO₃ (mmol/L) [PaCO₂ (mmHg)]	$24 + \frac{\text{PaCO}_2 - 40}{10}$	$24 + \left(\frac{\text{PaCO}_2 - 40}{10}\right) \times 4$	$24 - \left(\frac{40 - \text{PaCO}_2}{10}\right) \times 2$	$24 - \left(\frac{40 - \text{PaCO}_2}{10}\right) \times 5$

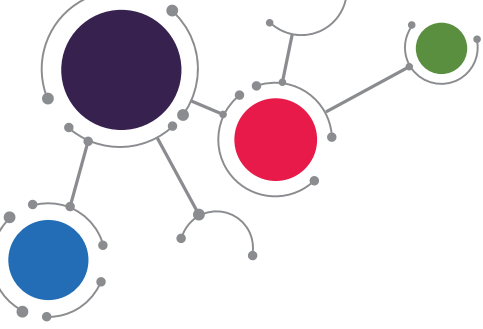
MANAGEMENT

- 1 Provide supportive treatment with oxygen, i.v. fluids and treat symptomatic hyperkalaemia.
- 2 Correct any reversible underlying disorder:
 - (i) Administer fluid and insulin, and replace potassium in diabetic ketoacidosis.
 - (ii) Ensure adequate oxygenation and restore the intravascular volume to improve peripheral perfusion in lactic acidosis.
- 3 Refer the patient to the medical team. Dialysis will be necessary for renal failure and severe methanol or salicylate poisoning.

METABOLIC ALKALOSIS

DIAGNOSIS

- 1 An abnormal process or condition leading to a serum bicarbonate level of >28 mmol/L.
- 2 Causes include:
 - (i) Addition of base to extracellular fluid:
 - (a) recovery from organic acidosis secondary to metabolism of lactate and acetate
 - (b) milk-alkali syndrome (excess antacids)
 - (c) massive blood transfusion (metabolism of citrate).



3 :: ACID-BASE DISTURBANCES

- (ii) Chloride depletion:
 - (a) loss of gastric acid from vomiting or gastric aspiration
 - (b) diuretics.
 - (iii) Potassium depletion:
 - (a) primary (Conn's) and secondary hyperaldosteronism
 - (b) Cushing's or Bartter's syndromes
 - (c) severe hypokalaemia.
 - (iv) Other:
 - (a) laxative abuse
 - (b) severe hypoalbuminaemia.
- 3 The body compensates to reduce the bicarbonate load by hypoventilation. The expected compensatory rise in PaCO_2 may be calculated ([see Table 3.2](#)).
- (i) This effect can be pronounced. Compensatory arterial PaCO_2 levels as high as 86 mmHg (11.5 kPa) have been recorded.
 - (ii) However, this compensatory PaCO_2 elevation is variable:
 - (a) pain or hypoxia cause the respiratory rate to rise and the PaCO_2 to fall, thereby worsening the alkalosis.
- 4 There are few specific clinical features other than hypoventilation. Symptoms relating to associated hypocalcaemia (tetany) and hypokalaemia (weakness) may be present.

MANAGEMENT

- 1 Give high-flow oxygen to reduce complications associated with hypoventilation. Try to avoid hyperventilation, as this worsens the alkalaemia.
- 2 Correct any reversible underlying disorder.
- 3 Administer normal saline at 500 mL/h i.v. to replace lost chloride, restore intravascular volume, and enhance renal bicarbonate excretion.
- 4 Replace potassium with potassium chloride 10–20 mmol/h i.v. if the potassium is low.
- 5 Consider the use of acetazolamide 250 mg orally to increase the rate of bicarbonate elimination.



3 :: ACID-BASE DISTURBANCES

RESPIRATORY ACIDOSIS

DIAGNOSIS

- 1 A primary acid–base disorder associated with respiratory failure, inadequate alveolar ventilation and an arterial $\text{PaCO}_2 > 45$ mmHg (6.0 kPa).
- 2 Causes include:
 - (i) Loss of central respiratory drive:
 - (a) drugs, e.g. opiates, sedatives, anaesthetic agents
 - (b) cerebral trauma, tumour, haemorrhage or stroke.
 - (ii) Neuromuscular disorders:
 - (a) Guillain–Barré syndrome, myasthenia gravis
 - (b) toxins, e.g. organophosphate poisoning and snake venom.
 - (iii) Respiratory compromise:
 - (a) chronic obstructive pulmonary disease (COPD), critical asthma, restrictive lung disease
 - (b) pulmonary oedema, aspiration, pneumonia
 - (c) upper airway obstruction and laryngospasm
 - (d) thoracic trauma, pneumothorax, diaphragm splinting
 - (e) high thoracic or cervical spinal cord trauma
 - (f) morbid obesity.
- 3 Clinical manifestations of respiratory acidosis are secondary to the hypercapnoea. Look for the following:
 - (i) The patient is usually warm, flushed, sweaty and tachycardic with ‘bounding’ peripheral pulses, from cardiovascular stimulation.
 - (ii) Acute confusion, mental obtundation, somnolence and occasionally focal neurological signs from increased cerebral blood flow, cerebral vasodilation and raised intracranial pressure.
- 4 The body compensates to reduce acidaemia by minimizing the excretion of bicarbonate by the kidneys. However, this renal compensatory response is slow.
 - (i) There is no time for any significant renal compensatory response in an acute respiratory acidosis.
 - (ii) The kidneys are able to retain bicarbonate in chronic respiratory acidosis



3 :: ACID-BASE DISTURBANCES

WARNING!

The pulse oximeter may record a normal oxygen saturation in a patient receiving supplemental oxygen, despite the presence of dangerous hypercapnoea from hypoventilation.

lasting over a few days, so the plasma bicarbonate level rises and the pH returns towards normal.

(iii) The expected compensatory rise in plasma bicarbonate in acute and chronic respiratory acidosis may be calculated (see Table 3.2).

MANAGEMENT

- 1 Give oxygen and commence assisted ventilation by bag-mask ventilation. Call for senior emergency department (ED) doctor help and prepare for emergency endotracheal intubation, or non-invasive ventilation such as continuous positive airway pressure (CPAP), for instance in acute pulmonary oedema.
- 2 Correct any reversible underlying disorder, e.g. naloxone for opiate poisoning.

RESPIRATORY ALKALOSIS

DIAGNOSIS

- 1 A primary acid-base disturbance, associated with increased alveolar ventilation and an arterial PaCO_2 of <35 mmHg (4.7 kPa).
- 2 Causes include:
 - (i) Asthma, pneumonia, pulmonary embolus, pulmonary oedema and pulmonary fibrosis (mediated by intrapulmonary receptors).
 - (ii) Hypoxia (mediated by peripheral chemoreceptors).
 - (iii) Centrally induced hyperventilation secondary to respiratory centre stimulation:
 - (a) head injury, stroke
 - (b) fever (cytokines), pregnancy (progesterone), thyrotoxicosis, liver disease
 - (c) drugs, e.g. salicylate poisoning
 - (d) pain, fear, stress, psychogenic, voluntary.
 - (iv) Iatrogenic from excessive artificial ventilation.
- 3 Clinical manifestations are secondary to hypocapnoea, hypokalaemia and hypocalcaemia. Look for the specific effects of hypocapnoea:
 - (i) Circumoral paraesthesia, carpopedal spasm and tetany from neuromuscular irritability.
 - (ii) Light-headedness and confusion from cerebral vasoconstriction (usually adapts in 6–8 h).

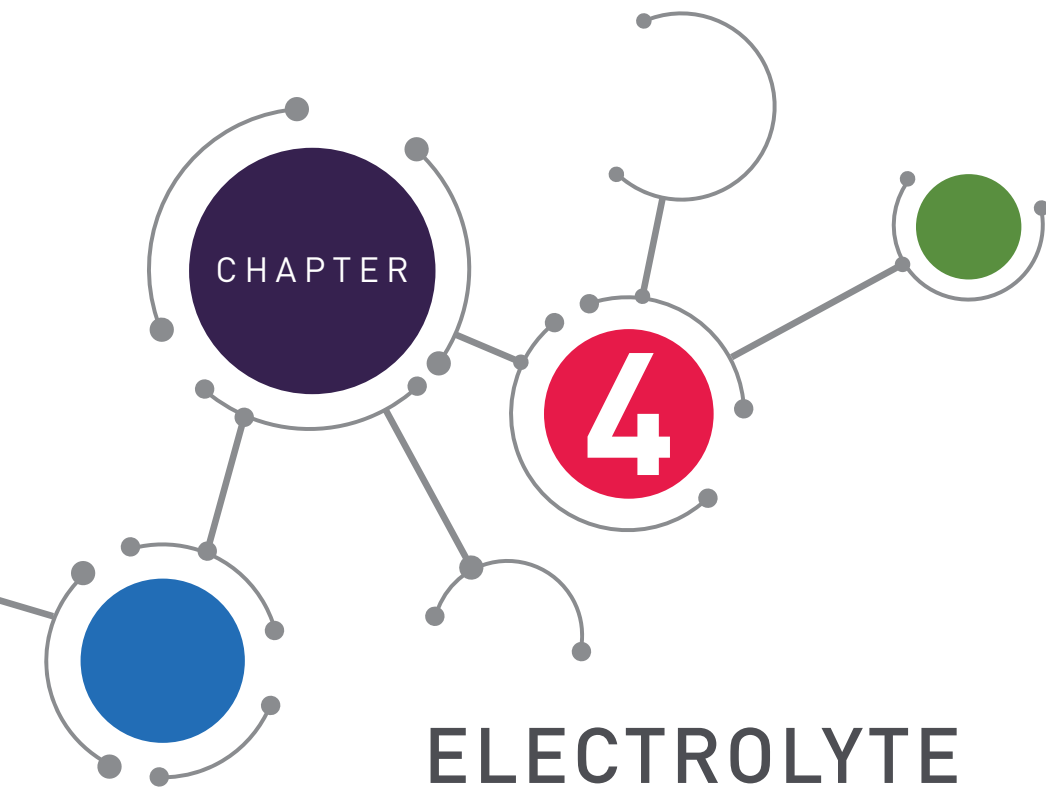


3 :: ACID-BASE DISTURBANCES

- (iii) Cardiac arrhythmias and decreased myocardial contractility.
- 4 The body compensates to reduce alkalaemia by excreting or buffering bicarbonate ions.
 - (i) A moderate compensatory response via a non-renal-mediated buffering process can reduce plasma bicarbonate levels to 18–20 mmol/L in an acute respiratory alkalosis within hours.
 - (ii) The kidneys increase the rate of bicarbonate excretion in chronic respiratory alkalosis, and reduce serum bicarbonate levels to as low as 12–15 mmol/L returning the pH towards normal
 - (a) this renal compensatory response is slow. The maximal effect takes 2–3 days to occur.
 - (iii) The expected compensatory fall in plasma bicarbonate in acute and chronic respiratory alkalosis may be calculated ([see Table 3.2](#)).

MANAGEMENT

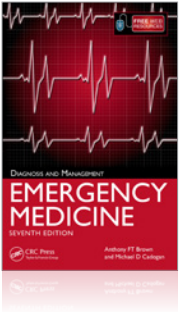
- 1 Give oxygen to treat any coexistent hypoxia.
- 2 Look for and correct any reversible underlying disorder.
- 3 Never diagnose 'hysterical' hyperventilation until subtle presentations of pneumonia, pulmonary embolism, pneumothorax, fever, etc., have been actively excluded.
- 4 Otherwise if no significant underlying cause for hyperventilation is likely, reassure the patient and/or ask them to rebreathe into a paper bag.



ELECTROLYTE DISORDERS



4 :: ELECTROLYTE DISORDERS



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Electrolyte disturbances are commonly associated with cardiovascular emergencies and may cause cardiac arrhythmias and cardiopulmonary arrest. Prompt recognition and immediate treatment of electrolyte disorders can prevent cardiac arrest.

POTASSIUM DISORDERS

The potassium gradient across the cellular membrane is essential to maintain excitability of nerve and muscle cells, including the myocardium.

Extracellular potassium levels are strictly regulated between 3.5 and 5.0 mmol/L and may be affected by many processes including serum pH.

As the pH rises, serum potassium falls as potassium is shifted intracellularly; when serum pH decreases, serum potassium increases as intracellular potassium shifts into the vascular space.

HYPERKALAEMIA

DIAGNOSIS

- 1 This is the most common electrolyte disturbance associated with cardiac arrest.
- 2 Causes include:
 - (i) Increased potassium intake:
 - (a) oral or i.v. potassium supplements, transfusion of stored blood.
 - (ii) Increased production:
 - (a) burns, ischaemia, haemolysis
 - (b) rhabdomyolysis, tumour lysis syndrome
 - (c) intense physical activity.
 - (iii) Decreased renal excretion:
 - (a) acute or chronic renal failure
 - (b) drugs, e.g. potassium-sparing diuretics, angiotensin converting enzyme (ACE) inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs)
 - (c) Addison's disease, hypoadosteronism.
 - (iv) Transcellular compartmental shift:
 - (a) acidosis (metabolic or respiratory)



4 :: ELECTROLYTE DISORDERS

TIP!

Consider hyperkalaemia in any patient with an arrhythmia or in cardiac arrest.

- (b) hyperglycaemia
 - (c) digoxin poisoning, suxamethonium.
 - (v) Factitious:
 - (a) haemolysed specimen, thrombocytosis, massive leucocytosis.
- 3 The risk of adverse events associated with hyperkalaemia increases with the serum concentration level. The severity of hyperkalaemia may be defined by the serum potassium level:
 - (i) Mild hyperkalaemia: potassium >5.5 mmol/L.
 - (ii) Moderate hyperkalaemia: potassium 6.0–6.5 mmol/L.
 - (iii) Severe hyperkalaemia: potassium >6.5 mmol/L.
 - 4 Patients may present with weakness, ascending paralysis, loss of deep tendon reflexes, and respiratory failure.
 - 5 Gain i.v. access and attach an electrocardiography (ECG) monitor and pulse oximeter to the patient.
 - 6 Look for the characteristic ECG changes that are usually progressive and determined by the absolute serum potassium, as well as its rate of increase:
 - (i) Tall, peaked (tented) T waves.
 - (ii) Prolonged PR interval with flattened P waves.
 - (iii) ST segment depression.
 - (iv) QRS widening, absent P waves and sinusoidal wave pattern.
 - (v) Ventricular tachycardia and cardiac arrest from ventricular fibrillation, pulseless electrical activity (PEA) or asystole.

MANAGEMENT

- 1 Give high-flow oxygen via face mask. Cease any exogenous sources of potassium supplementation.
- 2 **Severe hyperkalaemia** (>6.5 mmol/L) or hyperkalaemia with life-threatening ECG changes.

Provide immediate cardioprotection to prevent cardiac arrest:

- (i) Give 10% calcium chloride 10 mL i.v. over 2–5 min, repeated until the ECG and cardiac output normalize

(a) this does not lower the potassium level, but antagonizes the deleterious



4 :: ELECTROLYTE DISORDERS

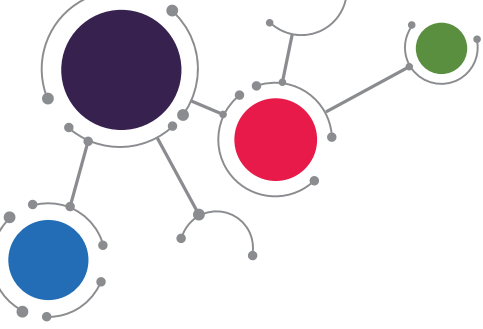
effects of hyperkalaemia on the myocardium, reducing the risk of ventricular fibrillation (onset of protection in 1–3 min).

- (ii) Use the other therapies outlined below to shift potassium into the cells, and eliminate potassium from the body.
- 3 **Moderate hyperkalaemia** (6.0–6.5 mmol/L). Shift potassium intracellularly with:
- (i) 50% dextrose 50 mL i.v. with 10 units of soluble insulin over 20 min (onset of action 15 min, with maximal effect within 1 h).
 - (a) beware more rapid delivery of the 50% dextrose with the insulin as it may paradoxically release intracellular potassium due to its hypertonicity
 - (b) give the soluble insulin alone in hyperglycaemic patients with a blood sugar of >12 mmol/L (i.e. without the dextrose).
 - (ii) Salbutamol 10–20 mg nebulized. Several doses may be required (onset of action 15 min).
 - (iii) 8.4% sodium bicarbonate 50 mL i.v. over 5 min, provided there is no danger of fluid overload, as it contains 50 mmol sodium
 - (a) less effective as a sole agent, but works well in combination with salbutamol and dextrose/insulin (onset of action 15–30 min), and if a metabolic acidosis is present.
- 4 **Mild hyperkalaemia** (5.5–6.0 mmol/L). Remove potassium from the body with:
- (i) Frusemide (furosemide) 40–80 mg i.v. (onset of action with diuresis, provided not anuric).
 - (ii) Potassium-exchange resin: calcium resonium 30 g orally or by enema (onset of action 1–3 h after administration).
- 5 Refer the patient to the medical team, and according to the potassium level and underlying cause, organize urgent haemodialysis or peritoneal dialysis as needed, particularly in known renal failure.

HYPOKALAEMIA

DIAGNOSIS

- 1 Hypokalaemia is associated with an increased incidence of cardiac arrhythmias especially in those patients with pre-existing heart disease, and in those treated with digoxin.
- 2 Causes include:
 - (i) Inadequate intake of potassium, e.g. alcoholism, starvation.



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TIP!

Consider hypokalaemia in any patient with an arrhythmia or in cardiac arrest.

- (ii) Abnormal gastrointestinal losses from vomiting, diarrhoea and laxative abuse.
 - (iii) Abnormal Renal Losses:
 - (a) Cushing's, Conn's and Bartter's syndromes
 - (b) ectopic adrenocorticotrophic hormone (ACTH) production
 - (c) drugs, e.g. diuretics and steroids
 - (d) hypomagnesaemia.
 - (iv) Compartmental shift:
 - (a) Hypomagnesaemia.
 - (b) metabolic alkalosis
 - (c) insulin
 - (d) drugs, e.g. salbutamol, terbutaline, aminophylline
- 3 Hypokalaemia occurs when serum potassium level is <3.5 mmol/L and is defined as severe if the serum potassium is <2.5 mmol/L.
 - 4 Look for weakness, fatigue, leg cramps and constipation.
 - (i) Polydipsia, polyuria, rhabdomyolysis, ascending paralysis and respiratory compromise may develop as the potassium level falls.
 - 5 Gain i.v. access and attach an ECG monitor. Non-specific ECG changes include:
 - (ii) Flat or inverted T waves, prominent U waves.
 - (iii) Prolonged PR interval.
 - (iv) ST segment depression.
 - (v) Ventricular arrhythmias, including torsades de pointes.

MANAGEMENT

- 1 Replace potassium immediately in the following situations:
 - (i) Serum potassium <3.0 mmol/L.
 - (ii) Serum potassium 3.0–3.5 mmol/L in patients with chronic heart failure or cardiac arrhythmias, particularly if on digoxin or following myocardial infarction.
- 2 Give potassium 10–20 mmol/h i.v. under ECG control using a fluid infusion device, but do **not** exceed 40 mmol/h.
- 3 Give magnesium sulphate 10 mmol (2.5 g) diluted in 100 mL normal saline over



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30–45 min in severe or intractable hypokalaemia, as magnesium enhances potassium uptake and helps maintain intracellular potassium levels.

- 4 Change to oral supplements or maintenance i.v. replacement when the serum potassium is >3.5 mmol/L.
- 5 Refer the patient to the medical team as necessary for treatment of the underlying condition.

SODIUM DISORDERS

Sodium is the most common intravascular cation. It has a major influence on serum osmolality and determines the volume of the extracellular fluid.

HYPERNATRAEMIA

DIAGNOSIS

- 1 Hyponatraemia is defined as a serum sodium level of >145 – 150 mmol/L.
- 2 Causes include:
 - (i) Decreased fluid intake with normal fluid loss:
 - (a) disordered thirst perception, e.g. hypothalamic lesion
 - (b) inability to communicate water needs, e.g. cerebrovascular accident, infants, intubated patients.
 - (ii) Hypotonic fluid loss, with water loss in excess of salt loss:
 - (a) skin loss from excessive sweating in hot climates, dermal burns
 - (b) gastrointestinal loss from diarrhoea or vomiting
 - (c) renal loss from impaired salt-concentrating ability, e.g. diabetes insipidus, osmotic diuretic agents, hyperglycaemia, hypercalcaemia, chronic renal disease.
 - (iii) Increased salt load:
 - (a) hyperaldosteronism or Cushing's syndrome
 - (b) ingestion of seawater, salt tablets, and administration of sodium bicarbonate or hypertonic saline.
- 3 Symptoms and signs of hyponatraemia are progressive and directly related to the serum osmolality level. Look for:
 - (i) Increased thirst, weakness, lethargy and irritability (>375 mOsm/kg).



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- (ii) Altered mental status, ataxia, tremor and focal neurological signs (>400 mOsm/kg).
- (iii) Seizures and coma (>430 mOsm/kg).
- 4 Assess the underlying volume status. Look at the skin turgor, jugular venous pressure (JVP), measure lying and sitting blood pressures, listen for basal crackles.
- 5 Send blood for full blood count (FBC), U&Es, liver function tests (LFTs), and serum osmolality.
- 6 Perform an ECG and request a chest radiograph (CXR).

MANAGEMENT

- 1 Give high-flow oxygen via a face mask.
- 2 Replace fluid orally, or via a nasogastric tube in stable asymptomatic patients.
- 3 Give hypovolaemic patients volume replacement with i.v. normal saline without causing too rapid a reduction in the serum sodium.
 - (i) Aim to reduce serum sodium by 0.5–1.0 mmol/L per h.

HYPONATRAEMIA

DIAGNOSIS

- 1 Hyponatraemia is defined by a serum sodium level <130 mmol/L.
- 2 Causes include:
 - (i) **Factitious 'pseudohyponatraemia'**
 - (a) associated with hyperglycaemia, hyperlipidaemia, hyperproteinaemia
 - (b) correct the sodium for hyperglycaemia by adjusting the serum sodium up by 1 mmol/L for every 3 mmol/L elevation in blood sugar.
 - (ii) **Hypovolaemic hyponatraemia**
 - (a) urinary sodium >20 mmol/L: renal causes including diuretics, Addison's disease, salt-losing nephropathy, glycosuria, ketonuria
 - (b) urinary sodium <20 mmol/L: extrarenal losses such as vomiting, diarrhoea, burns, pancreatitis.
 - (iii) **Normovolaemic hyponatraemia**
 - (a) urine osmolality $>$ serum osmolality:
 - syndrome of inappropriate antidiuretic hormone secretion (SIADH) due



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to head injury, meningoen­cephalitis, CVA, pneumonia, COPD, neoplasia, human immunodeficiency virus (HIV) infection, drugs such as carbamazepine, NSAIDs and antidepressants such as SSRIs

- positive-pressure ventilation, porphyria

(b) urine osmolality < serum osmolality:

- hypotonic post-operative fluids such as 5% dextrose or 4% dextrose 1/5 normal saline, transurethral resection of the prostate (TURP) irrigation fluid, psychogenic polydipsia, 'tea and toast' diet, beer potomania.

(iv) **Hypervolaemic hyponatraemia**

(a) urinary sodium <20 mmol/L: congestive cardiac failure, cirrhosis, nephrotic syndrome, hypoalbuminaemia, hepatorenal syndrome

(b) urinary sodium >20 mmol/L: steroids, cerebral salt wasting, chronic renal failure, hypothyroidism.

3 Clinical features progress as the serum sodium level drops, but depend also on the rate of fall, i.e. the more rapid the fall the greater the symptoms:

- (i) Na >125 mmol/L: usually asymptomatic.
- (ii) Na 115–125 mmol/L: lethargy, weakness, ataxia, and vomiting.
- (iii) Na <115 mmol/L: confusion, headache, convulsions, and coma.

4 Assess the underlying volume status:

- (i) Look at the skin turgor, jugular venous pressure (JVP), measure lying and sitting blood pressure (BP), listen for basal crackles.

5 Send blood for FBC, U&Es, LFTs, thyroid function and serum osmolality. Send urine for sodium and osmolality.

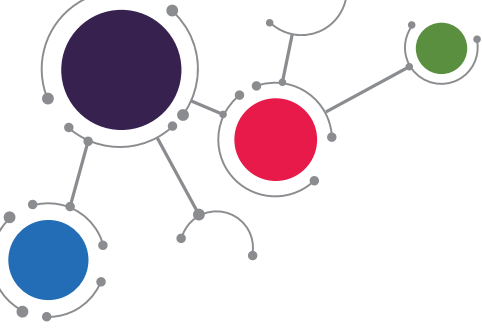
6 Perform an ECG and request a CXR.

MANAGEMENT

1 Commence high-flow oxygen by face mask.

2 Asymptomatic patients:

- (i) Discontinue implicated drug therapy and treat the underlying medical condition, e.g. antibiotics for sepsis.
- (ii) Restrict fluid intake to 50% of estimated maintenance fluid requirements in SIADH, i.e. around 750 mL/day.
- (iii) Aim to increase the serum sodium gradually by 0.5 mmol/L per h, to a maximum rate of 12 mmol/L per 24 h.



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WARNING!

Too rapid correction of hyponatraemia may cause coma associated with osmotic demyelination syndrome or central pontine demyelination, or the underlying disease process itself.

- 3 Get senior ED doctor help if the patient has neurological symptoms.
 - (i) Administer 3% hypertonic saline at 1–2 mL/kg/h to raise serum sodium levels by 1 mmol/L/h.
 - (ii) Aim to initially raise the serum sodium level by no more than 4–6 mmol/L.
 - (iii) Consult with the intensive care team if the patient develops seizures or coma.

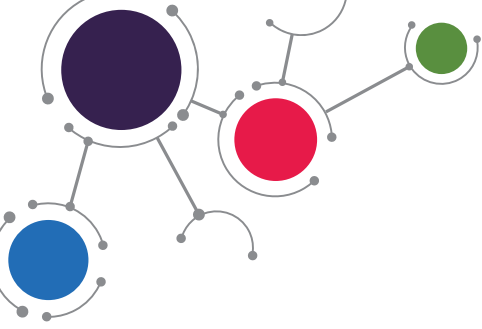
CALCIUM DISORDERS

Calcium is the most abundant mineral in the body and essential for bone strength, neuromuscular function and a myriad of intracellular processes. Minor degrees of hypercalcaemia may be the first clue to an underlying diagnosis of malignancy or hyperparathyroidism.

HYPERCALCAEMIA

DIAGNOSIS

- 1 Hypercalcaemia is defined by a serum calcium level of >2.6 mmol/L after correction for albumin.
- 2 Causes include:
 - (i) Malignancy, myeloma, sarcoidosis, thyrotoxicosis and tuberculosis.
 - (ii) Primary or tertiary hyperparathyroidism.
 - (iii) Drugs, e.g. thiazides.
 - (iv) Addison's disease.
- 3 Patients present with anorexia, thirst, weakness, abdominal pain, constipation, lethargy and confusion or psychosis. Coma may occur at serum calcium levels of >3.5 mmol/L.
- 4 Insert a large-bore i.v. cannula and send blood for FBC, U&Es, LFTs, calcium, lipase and thyroid function.
- 5 Perform an ECG. Typical changes include:
 - (i) Bradycardia.
 - (ii) Short QT interval with a widened QRS.
 - (iii) Flattened T waves, atrioventricular block and cardiac arrest.
- 6 Request a CXR that may show an underlying cause.



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MANAGEMENT

- 1 Commence rehydration with 0.9% normal saline i.v. at 500 mL/h.
- 2 Give frusemide (furosemide) 20–40 mg i.v. once urine output is established to maintain a diuresis.
- 3 Refer the patient to the medical team for longer-term therapy with steroids, bisphosphonates or dialysis.

HYPOCALCAEMIA

DIAGNOSIS

- 1 Hypocalcaemia is defined by a serum calcium level of <2.1 mmol/L after correction for albumin.
- 2 Causes include:
 - (i) Chronic renal failure, acute pancreatitis.
 - (ii) Rhabdomyolysis, tumour lysis syndrome, whole blood transfusion and toxic shock syndrome.
 - (iii) Primary respiratory alkalosis (hyperventilation).
 - (iv) Post-parathyroidectomy or thyroid surgery; autoimmune hypoparathyroidism.
- 3 Patients present with paraesthesiae of the extremities and face, muscle cramps, carpedal spasm, stridor, tetany, seizures and cardiac failure.
- 4 Look for hyper-reflexia and a positive Chvostek's or Trousseau's sign:
 - (i) Chvostek's sign: facial twitching from percussing the facial nerve in front of the ear.
 - (ii) Trousseau's sign: carpal spasm after 3 min of inflation of a BP cuff above systolic pressure.
- 5 Insert a large-bore i.v. cannula and send blood for FBC, U&Es, LFTs, creatine kinase (CK), magnesium and lipase.
- 6 Perform an ECG and look for:
 - (i) QT interval prolongation, T wave inversion.
 - (ii) AV block, torsades de pointes (cardiac arrest may ensue).

MANAGEMENT

- 1 Commence rehydration with 0.9% normal saline i.v. at 250 mL/h.



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- 2 Look for and treat the underlying cause.
- 3 Give calcium i.v. in symptomatic patients:
 - (i) 10% calcium chloride 10–40 mL i.v.
 - (ii) discuss further elemental calcium infusion with the medical team or intensive care unit (ICU) admitting team.
- 4 Give calcium by oral calcium supplements, or vitamin D-rich milk in asymptomatic patients.

MAGNESIUM DISORDERS

Magnesium is the second most abundant intracellular cation and essential for stabilizing excitable cellular membranes and facilitating the movement of calcium, potassium and sodium into and out of cells.

HYPERMAGNEAEMIA

DIAGNOSIS

- 1 Hypermagnesaemia occurs at a serum level of >1.1 mmol/L.
- 2 Causes include:
 - (i) Renal failure.
 - (ii) Iatrogenic magnesium administration i.v.
 - (iii) Rhabdomyolysis and tumour lysis syndrome.
- 3 Patients present with muscular weakness, respiratory depression, confusion, ataxia and hypotension.
 - (i) Extreme magnesium toxicity >5.0 mmol/L may be associated with bradycardia, respiratory depression, altered conscious level and cardiac arrest.
- 4 Insert a large-bore i.v. cannula and send blood for FBC, U&Es, LFTs, magnesium and thyroid function.
- 5 ECG changes are similar to hyperkalaemia.

MANAGEMENT

- 1 Commence i.v. rehydration with normal saline at 500 mL/h.
- 2 Give 10% calcium chloride 10 mL i.v. for life-threatening arrhythmias and severe magnesium toxicity.



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- 3 Otherwise give a combination of normal saline i.v. and frusemide (furosemide) 1 mg/kg i.v. to increase the renal excretion of magnesium, provided the urine output is normal.
 - (i) Check calcium levels regularly to prevent hypocalcaemia, which will worsen the symptoms of magnesium toxicity.
- 4 Refer the patient to the medical team or ICU for consideration of dialysis in severe toxicity with levels >5.0 mmol/L.

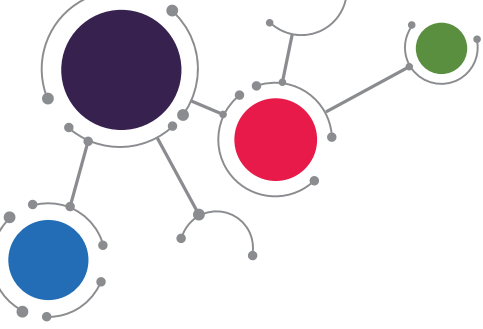
HYPOMAGNESAEMIA

DIAGNOSIS

- 1 Hypomagnesaemia occurs at a serum level of <0.6 mmol/L.
- 2 Causes include:
 - (i) Increased magnesium losses:
 - (a) gastrointestinal loss from vomiting, diarrhoea, pancreatitis
 - (b) acute tubular necrosis (ATN) or chronic renal failure
 - (c) drugs, e.g. alcohol, diuretics, gentamicin, cisplatin.
 - (ii) Reduced magnesium intake in starvation, malnutrition, chronic alcoholism.
 - (iii) Metabolic with low levels of calcium, phosphate and potassium.
 - (iv) Endocrine such as diabetic ketoacidosis (DKA), thyrotoxicosis, hyperparathyroidism, hypothermia.
- 3 Clinical manifestations are non-specific and may mimic hypocalcaemia and hypokalaemia. Look for tremor, paraesthesiae, tetany, altered mental state, ataxia, nystagmus and seizures.
- 4 Insert a large-bore i.v. cannula and send blood for FBC, U&Es, LFTs, CK, magnesium, lipase and thyroid function.
- 5 Perform an ECG and look for:
 - (i) Prolongation of PR and QT intervals.
 - (ii) ST segment depression.
 - (iii) Widened QRS and torsades de pointes.

MANAGEMENT

- 1 Commence rehydration with 0.9% normal saline i.v. at 250 mL/h.



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- 2 Look for and treat the underlying cause.
- 3 Administer oral magnesium supplements to asymptomatic patients.
- 4 Start parenteral magnesium in more severe cases:
 - (i) Give patients with seizures, torsades de pointes, or cardiac arrest 50% magnesium sulphate 8 mmol or 2 g i.v. over 2–5 min.
 - (ii) Give other symptomatic patients 50% magnesium sulphate 8 mmol (2 g) i.v. at a slower rate over 10–15 min.
- 5 Refer the patient to the medical team and discuss further elemental magnesium treatment.