Oliguria and acute kidney injury

Clinical problems

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LEARNING OBJECTIVES

After studying this module on Oliguria and Acute Kidney Injury, you should be able to:

1. Recognise and resuscitate the oliguric patient
2. Determine the diagnosis in an oliguric patient
3. Effectively treat the oliguric patient
4. Comprehend the pathophysiologic mechanisms of different causes of oliguria/AKI

FACULTY DISCLOSURES

The authors of this module have not reported any disclosures.

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DURATION

7 hours

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Introduction

The evolution of the term ‘acute renal failure’ dates back to 1802, when William Heberden first described it as Ischuria Renalis. Since then there are over 35 official definitions of the term; these include: acute Bright’s disease, war nephritis and crush syndrome. It wasn’t until 1951 that Homer W. Smith introduced the term ‘acute renal failure’.

Today, acute kidney injury (AKI) is considered the correct nomenclature for the clinical disorder formerly termed ‘acute renal failure’ (ARF). AKI is a common clinical problem in critically ill patients that is associated with increased morbidity and mortality. Even a modest impairment in renal function is an independent risk factor for mortality, but the onset of AKI is often not recognised.


In order to stage the severity of AKI, a graded classification, known as the RIFLE criteria (risk, injury, failure, loss, ESRD) was established. The RIFLE criteria incorporate levels of oliguria in addition to incremental serum creatinine elevations. The RIFLE criteria were later modified and referred to as the acute kidney injury network (AKIN) definition (see Table 1). Compared with the RIFLE classification, the AKIN definition includes lesser degrees of serum creatinine elevation to diagnose AKI, identical grades of oliguria, and a similar severity staging system. For all practical purposes, RIFLE and AKIN criteria are the same. The concept of AKI as defined by RIFLE/AKIN creates a new paradigm. Further validation studies may be required to confirm the RIFLE/AKIN criteria as a means of classifying patients with AKI but the current evidence is that categorising AKI patients by either RIFLE or AKIN severity criteria facilitates rational clinical management, is predictive of clinical outcomes and changes the way we view AKI.

Table 1

<table>
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<th>System</th>
<th>Class/Stage</th>
<th>Serum Creatinine Criteria</th>
<th>Urine Output Criteria</th>
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<td>RIFLE</td>
<td>Class R</td>
<td>Serum creatinine increase to 1.5-fold or GFR decrease &gt;25% from baseline</td>
<td>&lt;0.5 ml/kg/hour for 6 hours</td>
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<td>Class I</td>
<td>Serum creatinine increase to 2.0-fold or GFR decrease &gt;50% from baseline</td>
<td>&lt;0.5 ml/kg/hour for 12 hours</td>
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<tr>
<td></td>
<td>Class F</td>
<td>Serum creatinine increase to 3.0-fold, GFR decrease &gt;75% from baseline or serum creatinine ≥354 µmol/l (&gt;4.0 mg/dl) with an acute increase of at least 44 µmol/l (0.5 mg/dl)</td>
<td>&lt;0.3 ml/kg/hour for 24 hours or anuria for 12 hours</td>
</tr>
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<td>AKIN</td>
<td>Stage 1</td>
<td>Serum creatinine increase ≥ 264 µmol/l (≥0.3 mg/dl) or increase to 1.5-fold to 2.0-fold from baseline</td>
<td>&lt;0.5 ml/kg/hour for 6 hours</td>
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<tr>
<td></td>
<td>Stage 2</td>
<td>Serum creatinine increase &gt;2.0-fold to 3.0-fold from baseline</td>
<td>&lt;0.5 ml/kg/hour for 12 hours</td>
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<tr>
<td></td>
<td>Stage 3</td>
<td>Serum creatinine increase &gt; 3.0-fold from baseline or serum creatinine ≥354 µmol/l (≥4.0 mg/dl) with an acute increase of at least 44 µmol/l (0.5 mg/dl)</td>
<td>&lt;0.3 ml/kg/hour for 24 hours or anuria for 12 hours.</td>
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Need for RRT

**RIFLE and AKIN criteria for AKI classification and staging.** Adapted from Bellomo et al., and Mehta et al., with permission from the original publisher, BioMed Central. AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; GFR, glomerular filtration rate, RIFLE, Risk, Injury, Failure, Loss and End-Stage kidney disease; RRT, renal replacement therapy.

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Urine flow (urine output) is a vital sign in acute medicine; oliguria is defined as a urine output that is less than 1 mL/kg/h in infants, less than 0.5 mL/kg/h for six consecutive hours in children and adults. In critically ill patients, oliguria is often a sign of acute kidney injury that precedes serum creatinine increases and requires immediate attention.

However, oliguria and azotaemia are indicative not only of intrinsic kidney disease (ischaemic acute tubular necrosis [ATN]) but can also represent a normal response of the kidney to extracellular volume depletion (‘pre-renal’ state).

Oliguria should be presumed to be reversible and a prompt, active and analytical response is needed to prevent AKI progression. Initial resuscitation is followed quickly by an informed sequence of diagnostic and therapeutic interventions.

A key message of this module is that every effort is required to avert acute renal failure in the ICU, which is most commonly due to ATN caused by sepsis. If AKI is not prevented or reversed, the risk of a critically ill patient dying is increased considerably.

Acute kidney injury does not invariably present with oliguria: non-oliguric AKI occurs in 28-45% of the general ICU population but may be up to 50% of cases depending on the definition of AKI used, severity of illness and local practice patterns. Non-oliguric AKI in ICU patients is generally portrayed as having a better prognosis when compared with oliguric AKI, and thus, may lead to withholding renal replacement therapy in anticipation of recovery. However, in one study by Liangos et al., non-oliguric AKI was associated with higher in-hospital mortality. It is therefore important to identify non-oliguric AKI patients who might require early dialytic therapy and not to delay this important intervention.


1. **How do I recognise and resuscitate the oliguric patient?**

**Recognition**

As mentioned above, early clinical recognition of oliguria in adults requires the detection of urine flow of less than 0.5 ml/kg/h for six consecutive hours. The objective is to detect oliguria as soon as possible to identify pre-renal failure that can progress to ATN if not treated promptly. The recent RIFLE and AKIN classifications specify the duration of oliguria as >6h, >12h or >24h, recognising that the greater the duration of oliguria (increasing RIFLE class) the greater the severity of injury and hospital mortality. Studies applying both the urinary output criteria, in addition to the serum creatinine, increased the ability of the AKIN classification to predict mortality.


If oliguria is suspected, urinary output should be monitored hourly. In patients with urinary catheters in situ, an initial assessment of the urinary catheter’s position and patency should be performed. This can be achieved if indicated by ‘flushing’ the urinary catheter and examining the abdomen for a palpable bladder. Once the clinician has established there is no mechanical reason for the oliguria, further evaluation and diagnosis of oliguria should proceed. A full clinical history and physical examination can frequently identify events and/or disease processes that underlie AKI and suggest an underlying diagnosis.

Although the diagnosis of AKI currently relies on increased serum creatinine or a reduction in urine volume (oliguria), the recent emergence of novel AKI biomarkers is anticipated to aid the early diagnosis of AKI and is discussed in Task 2.

**Differential diagnosis**


The diagnosis of AKI into three distinct pathophysiological categories (pre-renal,
intrinsic renal and post-renal) is of real clinical utility. The clinical circumstance usually suggests the category of renal impairment (see Tasks 3 and 4 for treatment and aetiology).

**Pre-renal failure** (azotaemia) is most common among hospitalised patients. Pre-renal indicates that the cause lies outside the kidney, specifically ‘before’ the kidney. A history of high output gastrointestinal losses, haemorrhage, sepsis, congestive heart failure (CHF) and/or decreased oral intake resulting in hypovolaemia or a combination of these factors associated with hypotension and decreased urine output suggests AKI due to pre-renal disease (or ATN if persistent). When more than 10-15% of the circulating volume is lost, findings on physical examination may include: tachycardia, dry mucous membranes, hypotension, low central venous pressure, oliguria, peripheral hypoperfusion with altered mentation and cold clammy skin with delayed capillary return.

Causes of ‘*intrinsic*’ renal failure depend on the clinical setting. In the ICU, pre-renal failure is the most common diagnosis, usually from hypovolaemia or sepsis. A failure of haemodynamic restoration with a trial of fluid replacement to restore urine output and the exclusion of post-renal pathologies supports the diagnosis. Allergic interstitial nephritis, usually due to antibiotics may also be responsible. The topic of intrinsic renal disease is addressed in the PACT module on Acute renal failure and the textbook chapter below.


**PACT module on Acute renal failure**

**Post-renal** failure is due to urinary tract obstruction and accounts for <5% of cases of AKI. Patients with complete bilateral urinary tract obstruction may present with anuria (urine output <50 mL/day). Obstruction of the bladder neck is the most common cause of post-renal AKI and may complicate prostatic disease (e.g., hypertrophy, neoplasia, or infection), neurogenic bladder, or therapy with anticholinergic drugs. Less common causes of acute lower urinary tract obstruction include blood clots, calculi, and urethritis with spasm. The clinical assessment and diagnosis of obstructive uropathy are outlined in Task 2 of this module.

**Note** Persistent severe oliguria or anuria (lasting several weeks) should prompt suspicion of severe ATN (5% of survivors do not recover renal function) or cortical necrosis. Classically severe, prolonged renal hypoperfusion results in patchy focal tubular damage including necrosis and apoptosis of tubular cells.

**Resuscitation**

In most oliguric patients the cause is *pre-renal* (55-90%). There is broad consensus on the importance of fluid therapy in acute resuscitation. Many patients
with presumed ‘renal’ oliguria have an ischaemic element and a trial of expansion of the circulating volume may be warranted, even if only to avoid unnecessary aggravation of the ‘renal’ insult due to uncorrected hypoperfusion.


The ‘fluid challenge’ attempts to identify and treat pre-renal failure that can progress to ATN if not treated promptly. Fluids should be given early and targeted to haemodynamic end points, such as increases in mean arterial pressure, pulse pressure variation, cardiac output, central venous pressure (CVP), central venous oxygen saturation, pulmonary artery occlusion pressure (PAOP), urine output and improvements in lactic acidosis and skin perfusion. In selected cases, a comprehensive haemodynamic assessment (see ‘Diagnostic approach’ Task 2) is indicated.


Rivers et al. have shown that early fluid therapy (and inotropic support where necessary), when titrated to targeted endpoints, achieved a significantly greater urine flow, CVP and arterial pressure and a significantly reduced mortality (p=0.009) in patients with severe sepsis or septic shock attending Accident and Emergency.


Concurrent attention to diagnosis is important to confirm or deny the initial assumption and to guide subsequent therapy.

The choice of the type of fluid used for resuscitation in the critically ill remains controversial and usually involves a fluid challenge with either natural/artificial
colloids or crystalloids. These can be given as 10-15 ml/kg of crystalloid e.g. 0.9% saline or compound sodium lactate or non-protein colloid e.g. gelatin (not available in USA) or hetastarch delivered rapidly via one or two large bore (14G) intravenous cannulae. Fluid replacement should be continued as long as there is a haemodynamic response; hypervolaemia is avoided.

The rate of fluid administration is reduced substantially or even stopped, when cardiac filling pressures (CVP or pulmonary artery occlusion pressure) increase or plateau without concurrent haemodynamic improvement. If haemodynamic endpoints are not reached despite adequate fluid resuscitation, inotropic/vasoactive drugs should be considered (catecholamines, vasopressin, others).

As the volume of distribution is much larger for crystalloid balanced salt solutions than for colloids, resuscitation with crystalloids requires more fluid (three to four times) to achieve the same end points and is likely to result in more oedema.

However, current evidence indicates that the choice of fluid does not influence outcome. The SAFE study (see below) showed that 4% albumin was safe but not superior to saline (in similar infused volumes) in preventing death or need for dialysis. The use of either crystalloid or colloid for haemodynamic support of patients in the intensive care unit seems to be associated with equivalent outcomes.


The potential detrimental effect of hydroxyethyl starch (HES) on kidney function has become a major concern and is not without debate over recent years (Boldt, 2009, Hartog and Reinhart, 2009). HES preparations have a greater volume effect than that of albumin. However, their use has been associated with osmotic nephrosis and possibly medullary hypoxia. A further problem with HES may be tissue deposition and associated pruritus, which appears to be dose dependent. The recent publication of recommendations and guidelines by an international collaboration of the Critical Care Nephrology Working Group of the European Society of Intensive Care Medicine (ESICM) currently recommends avoiding higher-molecular-weight preparations of HES and dextrans in sepsis.


Task 1. How do I recognise and resuscitate the oliguric patient?


Wiedermann CJ. Hydroxyethyl starch—can the safety problems be ignored? Wien Klin Wochenschr 2004; 116(17–18): 583-594. PMID 15515874

A common adverse consequence of fluid resuscitation is ‘fluid overload’ and pulmonary oedema with significant reductions in lung function and oxygenation. A threshold may exist beyond which the perceived benefit of additional fluid therapy after resuscitation may be detrimental. A positive cumulative fluid balance has been shown in several studies to independently predict hospital morbidity and mortality.


Ventilated ICU patients are relatively protected against the immediate consequences of ‘fluid overload’, at least in the short term. For example, FiO₂ and/or PEEP can be increased to counteract the adverse effects of pulmonary congestion on gas exchange. PEEP is carefully titrated so as not to produce adverse haemodynamic effects which might further reduce renal blood flow.

If the neck veins are distended from the outset, a fluid challenge should only be used cautiously, if at all, since the patient is more likely to need inotropic support combined with a rapid diagnostic work-up to identify whether the cause is cardiogenic or obstructive (see Tasks 2 and 4 for diagnosis and aetiology). In the setting of ‘renal’ oliguria, removal of precipitating ischaemic or toxic factors is the immediate priority. If there is diagnostic doubt or a possibility of concurrent renal hypoperfusion, a cautious trial of volume loading is usually warranted. Failure to respond to measures aimed at reversing presumed ‘pre-renal’ oliguria is suggestive of ‘renal’ (or ‘post-renal’) oliguria (see diagnosis below).

Early recognition and treatment of obstruction in ‘post-renal’ oliguria will usually result in some degree of recovery of renal function. Superimposed infection (urosepsis) will require appropriate antibiotic therapy together with early release of obstruction.
2. **HOW DO I REACH A DIAGNOSIS IN THE OLIGURIC PATIENT?**


The assessment is primarily clinical using targeted history taking and physical examination. A sequence of supplementary testing, which includes blood investigations, bedside urinary (macroscopic) visualisation and subsequent dipstick, biochemical and microscopic examination of urine can assist with making a firm diagnosis. In cases of AKI where obstruction is suspected or which are unresponsive to a trial of fluid/haemodynamic therapy, an ultrasound examination of the kidneys, ureters and bladder is indicated.

It is important to be alert to the possibility that oliguria may be ‘renal’ or ‘post-renal’, as identification and correction of the cause(s) can be rapidly rewarding and avoids wasting time with ineffectual, and possibly inappropriate treatments, targeting presumed ‘pre-renal’ oliguria. For an overview of causes see Task 4.

**Clinical assessment**

As mentioned in Task 1, it is the clinical circumstance that suggests the category of renal impairment (pre-renal, intrinsic, post-renal), pre-renal failure (azotaemia) and ATN being the most important among critically ill patients. A history of trauma, haemorrhage, hypotension, sepsis or septic shock, congestive heart failure (CHF), anaphylactic shock, fasting, recent surgery, high output gastrointestinal losses, decreased oral intake or patients receiving diuretics suggests AKI due to ‘pre-renal’ disease.

In the clinical assessment of the oliguric patient, a comprehensive history, study of the observation chart, clinical examination and a review of recent investigations and drug therapies will be necessary.

Fluid requirements in trauma patients may be increased due to covert blood or fluid loss from the intravascular space, ‘third-space’ losses associated with major surgery or as a result of fever, systemic inflammation or rhabdomyolysis. Vasodilated patients e.g. due to sepsis may become relatively hypovolaemic.

Oliguria and circulatory dysfunction due to either a low cardiac output or to systemic inflammation with vasodilation and hypotension is relatively common in intensive care patients. Conditions such as myocardial infarction, pulmonary
embolism, anaphylaxis or perioperative complications in high-risk surgical patients are also common causes of oliguria and hypotension. For further information see Task 4 and the following link:

PACT module on High-risk surgical patients

A history of sepsis, prolonged hypotension, drug and nephrotoxin exposure will in most cases identify patients with ‘intrinsic’ renal failure and ATN. Although ischaemic and nephrotoxic injuries are dominant in the ICU setting, glomerular and vascular pathologies, interstitial nephritis and autoimmune pulmonary renal syndromes should be included in the differential diagnosis. See Task 4 and the reference below for further information.


A full clinical history and physical examination will often reveal the diagnosis in ‘post-renal’ oliguria. Findings may include a misplaced catheter, palpable bladder and tenderness of the suprapubic abdominal region. The clinical features of post-renal oliguria may, however, be obscured by abdominal or pelvic injuries, obesity, stupor, intoxication or anaesthesia (see below). Nevertheless their identification and rectification can often be relatively straightforward and rewarding. A failure to recognise such features may lead to serious mismanagement – see anecdote.

**ANECDOCTE**

At the time when it was believed that high dose frusemide (furosemide) had a role in converting oliguric to non-oliguric renal failure, an ICU patient whose blocked urethral catheter was not detected clinically, was given frusemide 2 g i.v. This resulted in a 16 litre diuresis over the eight hours following relief of the obstruction.

In ruling out a ‘post-renal’ aetiology, specific attention should be paid to:

**Prostatism**

Classic symptoms are well-known but intermittent or partial urinary tract obstruction, typically from insidious-onset benign prostatic hypertrophy may produce a pressure-mediated, nephrogenic, vasopressin-resistant diabetes insipidus. Polyuria may aggravate symptoms and confuse the diagnosis.

**Agitated patient**

In brain injured, encephalopathic, or sedated patients and in those with spinal cord injury or during residual spinal anaesthesia, urinary retention may be manifested
by agitation or heart rate and blood pressure instability, including unexplained hypertensive episodes.

**Bladder discomfort**

This symptom, suggestive of acute bladder outlet obstruction, may also be a useful adjunctive sign when confirming bladder distension by palpation. The bladder may not be easily palpable, especially, in the obese, the peri-partum patient or in those with trauma to the abdomen/pelvis or after laparotomy.

If a patient develops oliguria abruptly or if a blocked urinary catheter is suspected e.g. due to clot formation in a patient with recent haematuria, a trial of flushing the catheter should be performed under sterile conditions. Many doctors have been ‘caught out’ by an obstructed urinary catheter at some time in their career – see anecdote above.

**Trauma patients**

Anuria associated with blood at the urethral meatus, perineal ecchymosis and a high-riding prostate on rectal examination suggests urethral disruption.

**Urine diversion**

Be alert to the possibility that urine formation may be normal but there may be disruption or diversion of anatomical outlets e.g. ileal conduit, nephrostomy, vesicovaginal or vesicocolic fistula.

**Urosepsis**

Flank pain and tenderness may signify acute ureteric obstruction (renal colic), perhaps with associated infection. Urinary obstruction predisposes to infection. Recurrence of urosepsis, or failure to respond rapidly to standard antimicrobial and supportive measures, should alert the clinician to the possibility of urinary tract obstruction.

**Further investigations**

**Blood**

According to the AKIN/RIFLE criteria, the diagnosis of AKI is based on either elevation of serum creatinine or the presence of oliguria. Measurements of blood urea nitrogen and serum creatinine to assess glomerular filtration rate (GFR) are done daily in the ICU but can be monitored more frequently e.g. 12 hourly. A rise in serum creatinine is associated with a parallel decrease in GFR and generally implies a reduction in kidney function, and vice versa. The rate of change of urea and creatinine blood levels may differ in different pathologic situations and this change (of one relative to the other) can be used diagnostically (see appendix – biochemistry).
Where the units (mg/dL) are used e.g. in the US, a simple rule of thumb applies whereby a blood urea nitrogen (BUN)–creatinine ratio greater than 20 is considered suggestive of pre-renal azotaemia and less than 10 to 15, reflective of ATN.

**Note** Where SI units are used however, and urea rather than BUN is used, the measurement units for urea (mmol/L) and creatinine (mcmol/L) are different and the rule of thumb, if calculated, requires a conversion (see Appendix – biochemistry).

According to the AKIN criteria, even small changes in creatinine within 48 hours, defined as an absolute increase in serum creatinine of more than or equal to 26.4 micromol/litre (>0.3 mg/dl) per day or a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline) is an independent predictor of mortality from AKI (see ‘Outcome after Oliguria/AKI’ below).


**Q. What do you understand by the term ‘uraemia’?**

A. Uraemia is a clinical entity the principal characteristics of which in acute practice are encephalopathy, bleeding and pericarditis. All are life threatening e.g. the pericarditis may become haemorrhagic. Uraemia is an indication for dialysis. An elevated blood urea level is called ‘azotaemia’.

**Q. Other than serum urea, which blood test might be checked readily to support a presumed diagnosis of water depletion?**

A. Elevated serum sodium and haemoglobin levels are also indicative of water depletion. Serum osmolality provides more specific information.

**Q. In which situations might a deceptively low urea or creatinine level delay recognition of renal impairment?**

A. Creatinine may be deceptively low in patients with a small muscle mass e.g. in small elderly women. Urea may be deceptively low in those whose protein turnover is low e.g. in malnourished or liver failure patients.

Hyperkalaemia is a biochemical indicator of acutely deteriorating renal excretory capacity. Hyperkalaemia may be life threatening, or subject to a hyperacute rise e.g. due to concurrent rhabdomyolysis and is one of the recognised indications for urgent dialysis in acute renal impairment. Concurrent acidosis can aggravate hyperkalaemia. Hyperphosphataemia may also indicate failing excretory capacity and/or cellular destruction.
Other specific blood investigations can aid the diagnosis of primary glomerular diseases, these include: complement levels (C3,C4), anti-glomerular basement membrane antibody (aGBM), antineutrophil cytoplasmic antibodies (ANCA) levels, anti-streptolysin-O (ASO) titers.

**Note** Focused investigation based on the clinical evaluation is likely to be the most rewarding.

**Urine dipstick**

Certain patterns of bedside urinalysis are associated with intrinsic renal disease. Essential information includes specific gravity, the presence of proteinuria (glomerular injury), glycosuria (tubular injury), or haematuria (infection, nephrolithiasis, primary glomerular diseases). See appendix.

Q. Does the urinary dipstick differentiate between myoglobinuria and haemoglobinuria? Explain your answer.

**A.** No. Dipstick reaction is non-discriminatory in this respect. Orthotoluidene used in the dipstick interacts with the globin fragment of both myoglobin and haemoglobin. In trauma patients for example, haemolysis may confound attempts to use the urine dipstick to confirm myoglobinuria.

**Urine biochemistry and sediment analysis**

In ‘pre-renal’ oliguria, the urinary macroscopic appearance is concentrated, the dipstick specific gravity (SG) is high (>1.018), as is the osmolality (>350 mosm); the spot urine Na is low (<10 mmol/l) and the fractional excretion of sodium (FeNa) is reduced (<1%). These indices become unreliable once the patient has received diuretic therapy and may also be confounded by endogenous osmolar substances such as glucose or urea. FeUrea may be at least as reliable, if not more reliable than FeNa. The FeUrea appears more accurate in detecting pre-renal azotaemia, in particular in patients taking diuretics. Typical biochemical values associated with ‘intrinsic’ renal oliguria are: urinary sodium concentration (mmol/l) >20, FeNa (%) >1, urinary osmolality (mosm/l) <350. For fuller discussion, including reference to ‘renal failure index’ – see appendix (Task 5).

**References**


Some authorities advocate examining the urinary sediment; others do not. Hyaline and fine granular casts are common in pre-renal disease, ATN usually is associated
with coarse granular casts, muddy brown casts and tubular epithelial cell casts. The presence of red blood cell casts indicates glomerular disease. The urinary sediment in post-renal failure is often very bland in appearance, without casts. The discriminating ability of these findings is of limited practical value, particularly in the ICU setting. A systematic review of studies describing urinary biochemistry indices, and microscopy in AKI demonstrated significant variability and inconsistency in these measures. In fact, no single measure of urinary biochemistry, derived index, or pattern on microscopy can be used reliably to diagnose AKI or classify or predict the clinical course of AKI in septic patients. On the contrary, a study by Perazella et al., using a urinary scoring system based on the presence of casts and renal tubular epithelial cells was highly predictive of the final diagnosis of ATN. It is recommended that urinary biochemistry and microscopy is performed in patients with AKI, unresponsive to fluid and/or haemodynamic therapy, to exclude primary renal disease for which timely therapy is very important for outcome of renal failure.


Q. What causes of ‘renal’ oliguria are not associated with a high Urine Na concentration and high FeNa?

A. Not all causes of renal oliguria result in a high FeNa. Interstitial nephritis, acute glomerulonephritis and uric acid nephropathy have been reported in association with low FeNa.

Q. What pathologies are associated with ‘Muddy brown casts’, ‘Red cell casts’, ‘Eosinophils’ or ‘Crystals’ in urinary sediment?

A. Muddy brown casts are associated with acute tubular necrosis. Red cell casts are associated with glomerulonephritis. Eosinophils are associated with interstitial nephritis. Crystals may be urate crystals associated with tumour lysis syndrome and uric acid nephropathy.

Urine microscopy, although sometimes termed ‘the poor man’s biopsy’ may be especially useful diagnostically and in guiding therapy in ‘renal’ oliguria. Other investigations that may be useful in selected cases are renal biopsy (if not contraindicated by coagulopathy) and renal perfusion scanning. For further
information about urinalysis, urine biochemistry and urine microscopy see the appendix.

**Biomarkers of AKI**

Serum creatinine is widely used in the diagnosis of AKI and is considered to be specific but generally an insensitive biomarker of renal dysfunction. With the recognition of the importance of small changes in serum creatinine of >0.3 mg/dL (26.4 mcmol/L), the sensitivity of serum creatinine to detect early renal injury has improved. However, significant renal tubular injury can occur before such creatinine increments have had time to develop. Serum creatinine concentration is greatly influenced by changes in muscle mass and tubular secretion, body weight, race, age, sex, total body volume, drugs, muscle metabolism and protein intake. For these reasons it is generally considered a poor marker of early AKI and an even poorer reflection of kidney function because patients with AKI are not in steady state and serum creatinine therefore lags far behind renal injury. The recent development of novel biomarkers for the early detection of AKI promises to be a real advance in critical care and acute nephrology. The most promising of these include: NGAL (neutrophil gelatinase-associated lipocalin), IL-18, KIM-1, Cystatin C, and L-FABP.


Nickolas and colleagues examined the diagnostic properties of a single urinary NGAL level in 635 adults presenting to an inner city emergency department; 5% had AKI. Urinary NGAL distinguished AKI from other forms of kidney dysfunction and predicted excess morbidity after hospital admission. Logistic regression analysis demonstrated that NGAL was a better predictor of nephrology consultation, dialysis, ICU admission and death than other conventional or novel biomarkers of acute kidney injury. The AUROC (area under the receiver-operating characteristic) curves was 0.95, sensitivity was 0.900 (95% CI 0.730 to 0.980) and specificity was 0.995 (95% CI 0.990 to 1.000) for prediction of AKI using a cutoff value of 130 µg/g.


Another study by Koyner et al. evaluated both NGAL and cystatin C (CyC) as early biomarkers of AKI after adult cardiothoracic surgery. Both urinary CyC and urinary NGAL were elevated in those patients who later developed AKI, compared with those with no injury. The urinary NGAL at the time of intensive care unit arrival (AUC 0.700) and the urinary CyC level 6 h after ICU admission (AUC 0.724) were
most useful for predicting AKI. This study was also notable for the fact that plasma NGAL was a poor predictor of AKI (AUC 0.536) and plasma CyC also failed to diagnose AKI in the early postoperative period (AUC 0.624). Taken together these two studies and the studies listed below suggest the utility of urinary NGAL and CyC to diagnose AKI earlier than conventional methods.


With the inevitable introduction of the urinary and serum AKI biomarkers in clinical practice, the specific use of individual and combination biomarkers across patient cohorts e.g. septic patients, patients with pre-existing renal disease and other high-risk AKI clinical settings needs further investigation. On the basis of existing literature, serum but not urinary NGAL has limited capacity to detect early AKI in septic patients. The performance of biomarkers of AKI in patients with pre-existing renal disease with tubular damage has recently been studied. Many biomarkers, such as urinary NGAL and glutathione S-transferases, perform better in those with no history of chronic kidney disease. Continued comparison among the different AKI biomarkers across the different patient cohorts is essential for the ongoing development of the biomarkers in the evolving field of AKI and it is possible that ultimately an AKI biomarker package will emerge.


Q. List some of the roles and applications of NGAL in AKI?

A. NGAL can be useful for the early diagnosis of AKI in the following settings: cardiopulmonary bypass, contrast-induced nephropathy, sepsis in ICU and (early) after renal transplantation. A single urinary NGAL level was highly predictive for distinguishing AKI from normal renal function, pre-renal azotaemia and CKD.

Early NGAL measurements can predict the subsequent need for RRT, in-hospital mortality and response to therapy. Coincidentally, it has a role as a safety biomarker for monitoring drug toxicities in humans during the drug development process.

Imaging

Ultrasonography

Ultrasonography is a bedside, non-invasive investigation which avoids the need for administration of potentially nephrotoxic contrast media. The main purpose of the investigation is to diagnose or rule out an obstructive cause of oliguria. It also provides information on kidney size, enlarged kidneys being typical for AKI but small kidney(s) for chronic kidney disease. Papillary necrosis can be detected and might be useful in the diagnosis of analgesic nephropathy. Duplex sonography may distinguish between intrinsic and pre-renal disease.


Radiology

Plain films are useful for detecting kidney stones and calcification and for determining renal size. Hydroureter in ureterovesical junction obstruction and/or hydronephrosis due to obstruction at the pelviureteric junction may be seen. In bladder outlet obstruction, bilateral ureteric dilatation is seen.

CT renals

CT renal study is a useful non-contrast study to diagnose nephrolithiasis or pyelonephritis as a cause of acute kidney injury.

Q. What useful diagnostic information, other than the exclusion of renal obstruction, can ultrasound provide?

A. Ultrasound also provides information on kidney size. Small kidneys are suggestive of long-standing (rather than acute) renal disease. Congenital abnormalities e.g. polycystic
kidney disease and kidney agenesis may be diagnosed. Assessment of renal parenchymal appearance can provide information on renal cortex pathologies such as glomerulonephritis or cortical infarction. Duplex Doppler images of renal artery can provide further information on renal artery occlusion by embolus.

**Intravenous urogram**

This carries a risk of nephropathy caused by the intravenous contrast agent, particularly in diabetic patients. In severe obstruction, the nephrogram may be delayed, see Task 3.

**Retrograde and antegrade contrast studies**

Where the risk of contrast-induced nephropathy is great and when considering surgical intervention, retrograde or antegrade (urological/percutaneous) contrast studies, may be employed.

**Other tests**

**Haemodynamic assessment**

As discussed in Task 1 (Resuscitation), assessment of circulatory status may require central venous pressure monitoring (CVP), pulmonary artery catheterisation or other techniques for assessing cardiac output and filling pressures e.g. non-invasive measurement of cardiac output. Mixed venous oxygen saturation is used as an indirect indication of oxygen balance which can be affected by cardiac output, haemoglobin, arterial saturation and tissue oxygen consumption. Central venous oxygen saturation has been shown (by Rivers et al.) to be a useful early guide to targeted resuscitation in septic patients. Transthoracic or transoesophageal echocardiography (TOE) should be considered where greater knowledge of cardiac function is required for complete assessment. Targeted therapy entails frequent serial measurement and therapeutic adjustment.


PACT module on Haemodynamic monitoring

**Bladder pressure measurement**

Often an overlooked reason for acute oliguria is abdominal compartment syndrome defined as intra-abdominal pressure greater than 20 mmHg and abdominal perfusion pressure less than 60 mmHg occurring in association with a new and attributable organ dysfunction e.g. in a bleeding postoperative abdominal surgical patient or in those with severe ascites or other cause of acute abdominal distension. Abdominal compartment syndrome causes oliguria and AKI mainly by directly increasing renal outflow pressure and reducing renal perfusion.
Intra-abdominal hypertension is transmitted directly to the bladder and intravesical pressure also rises. The bladder pressure therefore reflects intrabdominal pressure and is the most commonly used mode of measurement.

Using the in-dwelling urinary catheter, no more than 25ml of sterile saline is infused into the bladder, following which intravesical pressure is measured using a water manometer or a pressure transducer connected to a side-port needle or three-way tap in the catheter system. Appropriately modified catheter systems are available. Sugrue has advocated a more standardised diagnostic approach to intra-abdominal pressure measurement and the international conference of experts (see reference below) has brought this forward.

See also PACT module on ‘Abdominal problems’


Intra-abdominal hypertension has a number of deleterious effects. Its Treatment and Understanding are considered in Task 3 and 4, respectively.
3. **HOW DO I TREAT THE OLIGURIC PATIENT?**


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**Note** The mainstay of treatment of oliguria is to ensure adequate renal perfusion through optimisation of volume status, cardiac output and systemic blood pressure.

Unfortunately, despite many advances in medical technology, the mortality and morbidity of AKI in the ICU remain high and have not improved significantly during the past two decades. This however, may reflect the likely increased illness severity of today’s cohort of ICU patients.

The treatment of oliguric AKI is supportive, requires identification and correction of precipitating factors but has no specific pharmacologic therapies. Supportive measures include maintenance of adequate renal perfusion with fluids and/or vasoactive drugs, avoidance of nephrotoxic agents, dose adjustment of renally excreted drugs and institution of renal replacement therapy (RRT) should an indication arise.

**‘Pre-renal’ oliguria**

**Supportive treatment**

Active supportive management is sometimes termed ‘renal rescue’ therapy. Optimisation of cardiac output and of renal perfusion pressure to restore an adequate renal blood flow is the essence of this approach.

**Fluid therapy**

As mentioned in the ‘resuscitation’ section in Task 1, the cause is ‘pre-renal’ in most oliguric patients and intravascular volume loading (using a titrated ‘fluid challenge’) is fundamental. For an overview of fluid therapy in oliguria see Task 1.

**Vasoactive and inotropic agents**

Despite adequate fluid resuscitation, many patients with circulatory shock have persistent hypotension. Hypotension, associated with shock can be the result of any of a number of factors e.g. intravascular hypovolaemia, (bi)ventricular dysfunction, vascular effects of the inflammatory response or a combination of these. Under these circumstances, potent systemic vasopressor agents, such as norepinephrine, epinephrine, inotropic doses of dopamine, phenylephrine or low-dose vasopressin or terlipressin have been used to restore an acceptable mean arterial blood pressure.
PACT module on Hypotension

The use of vasopressors is not without debate because of a belief that renal vasoconstriction is responsible for AKI and that such drugs may make renal vasoconstriction worse and induce more AKI. On the basis of currently available evidence in hypotensive vasodilated patients with AKI, restoring renal perfusion pressure is physiologically sound, especially in septic patients when some of the important autoregulatory mechanisms that help preserve GFR in the face of fluctuating blood pressure are disrupted.


Vasoactive agents

The choice of catecholamine depends on the clinical circumstance. There is no proven benefit of a particular vasoactive agent over another with regard to renal outcome; the key is to restore renal perfusion. Both dopamine and norepinephrine are widely used as first-line agents; other agents can be incorporated if the patient remains hypotensive and/or oliguric. Dopamine can cause tachycardias and arrhythmias, which may limit its use. Norepinephrine is as effective at raising blood pressure as dopamine, but has fewer cardiac side effects: it does not increase cardiac output as much as dopamine and causes less tachycardia.


De Backer et al. conducted a randomised multicentre trial in which patients received either dopamine or norepinephrine as first-line vasopressor therapy to treat circulatory shock (septic shock, cardiogenic shock or hypovolaemic shock). There was no significant difference in the rate of death between patients who were treated with dopamine and those treated with norepinephrine. However, arrhythmias were more frequent in the dopamine group. Among patients with
cardiogenic shock, the mortality at 28 days was higher in those treated with dopamine than in patients treated with norepinephrine. This study raises concerns about the safety of dopamine as a first-line therapy for cardiogenic shock.


Epinephrine can be used for hypotension, and has been shown to cause a rise in serum lactate levels due to stimulation of pyruvate production. In one randomised controlled study comparing epinephrine and norepinephrine in critically ill patients, there was no difference in achieving a MAP goal difference between the two agents and the 28 and 90-day mortality was similar in both groups. However, there was a higher incidence of drug-related side effects with epinephrine and this resulted in the withdrawal of epinephrine by attending clinicians in 12% of cases treated.


Vasopressin is commonly used as an adjunct to catecholamines to support blood pressure in refractory septic shock, but does not reduce mortality rates as compared with norepinephrine among patients with septic shock (VAASST investigators). In a post hoc analysis of the VAASST study, vasopressin was associated with a tendency to improved renal function, lower mortality and reduced requirement for renal replacement therapy in patients at ‘risk’ of acute kidney injury, but not in those who had already sustained significant renal injury. Further randomised trials are necessary to validate these observations.


The use of vasopressin and its synthetic analogues has other therapeutic indications in the ICU other than septic shock. Both vasopressin and terlipressin have shown beneficial effects in the management of patients with cirrhosis, especially in the context of variceal bleeding, the hepatorenal syndrome or both. In either case, current evidence suggest that terlipressin can produce a significant reduction in mortality. In patients with hepatorenal syndrome, systemic vasodilatation, in particular, splanchnic vasodilatation, is important in the activation of endogenous renal vasoconstrictors. These pathways, in turn, are believed to induce functional AKI. Accordingly, vasoconstrictors such as terlipressin may improve renal function by reducing splanchnic vasodilation and increasing central circulating blood volume and reducing endogenous renal vasoconstriction.


Taken together, and in view of the current lack of convincing evidence of the superiority of one vasoactive agent over another, an individualised approach is recommended.

Inodilation

Improved myocardial performance and vasodilatation is usually achieved using dobutamine, although dopexamine is an alternative but more vasodilatory agent. The classic indication for dobutamine is for the treatment of heart failure when the blood pressure is relatively normal. The accompanying vasodilation may precipitate hypotension (especially if the patient is hypovolaemic) but the increased cardiac output which is often associated with tachycardia usually compensates.

Levosimendan is a calcium sensitiser that can be used to treat patients with acute decompensated heart failure (ADHF). This drug enhances myocardial contractility without increasing myocardial oxygen use and does not appear to be proarrhythmic. In one meta-analysis from 27 randomised controlled studies, levosimendan was associated with a 4.8% reduction in mortality in critically ill patients. However, a large randomised controlled study is warranted to examine the effects of levosimendan on renal function in patients with ADHF.

**Dopamine receptor agonists**

**Q. What is meant by a ‘renal dose’ of dopamine? Give reasons as to why this is (or is not) a valid concept.**

**A.** It is not a meaningful clinical entity but the dose is usually quoted as 1–3 mcg/kg/min (also called ‘low-dose’ dopamine).

Low-dose dopamine is defined as the dose that produces preferential dopaminergic (and β-adrenergic effects) over α-adrenergic actions (<5 µg/kg/min) and thereby causes renal vasodilation and increases urinary output. Despite the widespread use of low-dose dopamine in oliguric patients over the past four decades, most evidence in favour of low-dose dopamine came from uncontrolled trials and anecdotal reports. Bellomo et al. performed the largest multicentre randomised controlled trial of low-dose dopamine (ANZICS study). In this study there was no difference between the dopamine and placebo groups in peak serum creatinine concentration during treatment. Low-dose dopamine by continuous IV infusion to critically ill patients at risk of renal failure does not seem to confer clinically significant protection from renal dysfunction.


In a comprehensive meta-analysis, Kellum and Decker showed that dopamine did not prevent the onset of acute renal failure or decrease mortality or the need for renal replacement therapy. Many authorities, having noted the lack of efficacy of ‘renal dose’ dopamine and the variety of associated adverse effects, now counsel strongly against using this agent.


Fenoldopam mesylate is a selective dopamine α-1 receptor agonist that can improve renal blood flow without increasing cardiac output because of its greater specificity for dopaminergic receptors and lack of activation of β-adrenergic receptors. In a small number of underpowered studies, fenoldopam has been associated with a decrease in risk of acute renal failure, need for renal replacement therapy and overall mortality. Until results from large randomised trials are available, the use of newer dopamine agonists, such as fenoldopam, should be considered experimental and not evidenced-based.
Q. What is the mechanism of the diuretic action of dopamine? Is the diuresis renoprotective?

A. Dopamine causes a natriuresis, the mechanism of which is threefold: improved renal blood flow and glomerular filtration due to elevated cardiac output and blood pressure (especially in heart failure patients), modification of intrarenal haemodynamics and via dopamine receptors at the level of the tubules. There is no evidence that a dopamine diuresis is renoprotective.

**Chronotropy**

Very occasionally chronotropic agents are useful if bradycardia is responsible for a low cardiac output and renal hypoperfusion. Cardiac pacing avoids pharmacotherapy and may be useful in some cases.

**Intra-aortic balloon counterpulsation**


Intra-aortic balloon counterpulsation (IABCP) can be useful in certain specific circumstances where there is reversible cardiac pathology e.g. acute (post-infarct) ventricular septal defect (VSD), mitral incompetence or myocardial dysfunction post cardiopulmonary bypass.

**Diuretics**

Diuretics are not a treatment for oliguria. They may be important in the management of volume overload or hyperkalaemia.

Volume overload may complicate the fluid challenge. Despite the lack of convincing evidence supporting their efficacy, the use of diuretic agents in oliguric renal failure is widespread. Numerous studies have evaluated loop diuretics in the treatment of AKI. The majority have failed to demonstrate clinical benefit. Diuretics do not alter the outcome of renal injury. Diuretics have traditionally been used to ‘convert’ the oliguric state to non-oliguric ATN.

A meta-analysis by Ho and Sheridan has shown that the use of diuretics in oliguric renal failure does not improve survival. The PICARD study group reported the results of a large prospective observational study of critically ill patients with AKI from 1989 to 1995. The study found that those patients with oliguric renal impairment who received diuretics had an increased risk of death or non-recovery of renal function. This increased risk associated with diuretic use was largely borne by those oliguric individuals who were relatively diuretic resistant and had a more severe form of renal failure. The use of diuretics in this setting should therefore be restricted to the treatment of volume overload and occasionally hyperkalaemia, and, even then, caution is advised as there is reasonable concern that excessive reliance on diuretics might delay initiation of RRT.

Ho KM, Sheridan DJ. Meta-analysis of frusemide to prevent or treat acute renal failure. BMJ 2006; 333(7565): 420. PMID 16861256


As mentioned in the ‘resuscitation’ section of Task 2, a common adverse consequence of fluid resuscitation is ‘fluid overload’ that may contribute to morbidity and mortality in the critically ill patient.


While diuretics are useful in managing volume overload, it is equally important to consider concurrent conservative treatments such as fluid restriction. Equally, in cases resistant to diuretic therapy and fluid restriction, initiation of renal replacement therapy for volume control needs to be considered. Once ultrafiltration is commenced, it is advised that diuretic therapy be discontinued to prevent hypovolaemia. For an overview on initiation of renal replacement therapy see PACT module on Acute renal failure.

Q. What are the commonest adverse effects of frusemide in acute care medicine?

A. Hypovolaemia, hypokalaemia and hypomagnesaemia; worsening renal insufficiency is also an acute risk. Hypernatraemia and contraction metabolic alkalosis may be associated with chronic frusemide use.
‘Renal’ oliguria

Specific treatment

Precipitating or aggravating factors are likely, despite supportive measures, to have a major influence on the course of the illness and require prompt correction where possible. These factors may include concurrent sepsis, rhabdomyolysis, intra-abdominal hypertension, hyperuricaemia associated with tumour lysis syndrome and drug effects.

Specific treatment for intrinsic renal disease e.g. immunosuppressive therapy for some forms of glomerulonephritis needs to be addressed once diagnosis has been made and other precipitating factors (‘pre’- and ‘post-renal’) have been excluded. For further discussion of these disease processes, see the PACT module on Acute renal failure.

Urinary alkalinisation (and mannitol, perhaps) have been advocated for rhabdomyolysis and myoglobinuria (see Task 4). Specific therapy is also indicated for urate nephropathy. Septic nephropathy requires early identification of the septic source, vigorous supportive treatment as well as eradication of the septic source with antimicrobials and surgery as indicated.


‘Post-renal’ oliguria

Transurethral catheterisation

Specific treatment for post-renal oliguria includes transurethral catherisation. This may be therapeutic, diagnostic or simply facilitative for patient monitoring. Catheterisation should be considered in all oliguric patients, provided there is no contraindication such as the suspicion of a ruptured urethra in trauma patients. An in-dwelling urinary catheter may be obstructed with debris or clot and require flushing or changing. In the case of intraluminal obstruction or extrinsic ‘kinking’ of the ureters, referral to urology or interventive radiology for ureteric catheterisation may be required.

Suprapubic catheterisation

If the bladder is distended and urethral catheterisation is not possible or is contraindicated, suprapubic catheterisation is favoured. This also applies where urethral damage from any cause or a false passage following unsuccessful catheterisation is suspected.
Percutaneous ultrasound-guided nephrostomy

Radiologic placement of a nephrostomy drainage tube may be beneficial, especially if the patient is too unstable for anaesthesia and urologic instrumentation. Complications include bleeding in the coagulopathic or thrombocytopaenic patient and the possibility of bacteraemia/sepsis secondary to instrumentation of an infected, obstructed kidney. If infection in the presence of obstruction is suspected, periprocedure antibiotic prophylaxis is warranted.

Abdominal compartment syndrome

As the pathology is partly ‘pre-renal’ in nature (see Task 4 – Understanding oliguria), initial treatment with an intravenous fluid challenge and/or inotropic therapy is indicated. Remember that the CVP may be artefactually raised due to transmission of the elevated IAP (intra-abdominal pressure) to the thoracic cavity. Despite correction of any ‘pre-renal’ element, oliguria and renal dysfunction may not improve and release of pressure may be indicated – see below.

Release of intra-abdominal pressure

If the development of a tense abdomen is accompanied by oliguria and the diagnosis is confirmed by elevated intravesical pressure, timely release of intra-abdominal hypertension (see Task 4), usually by (repeat) laparotomy and decompression, will often result in haemodynamic improvement and prompt restoration of urinary flow – sometimes the patient becomes polyuric. This approach, however, needs to be balanced against the potential adverse effects of laparotomy and alternative approaches e.g. bowel decompression or percutaneous drainage of infection sites may be appropriate; alternatives such as peritoneal catheter drainage, are being evaluated.


PACT module on Abdominal problems

To avoid recurrence of intra-abdominal hypertension, the laparotomy wound may be managed with delayed primary or secondary closure utilising, for example, a
barrier mesh to minimise fluid loss and serosal injury. A zipper is sometimes incorporated in the mesh to permit inspection, perhaps in the ICU, if no further surgical intervention is planned.

In a deteriorating intensive care patient with a suspected intra-abdominal collection, a contrast enhanced abdominal CT scan may be helpful and will require prophylaxis with IV hydration with either sodium bicarbonate or normal saline and administration of N-acetylcysteine. In the meta-analyses listed below, combination prophylaxis with NAC and sodium bicarbonate substantially reduced the occurrence of contrast-induced AKI overall but not dialysis-dependent renal failure. Combination prophylaxis should be considered for all high-risk patients (emergent cases or patients with chronic kidney disease) and for all interventional radiocontrast procedures.


Conservative treatment of acute kidney injury

Given the effect of AKI on mortality and the relative lack of specific pharmacological therapies, it is imperative that every effort be made to prevent AKI.

Conservative methods to minimise the risk of adding further insult to injury in patients with AKI include avoidance of nephrotoxic doses of antibiotics, use of non-ionic contrast agents or avoidance of a contrast study with non-contrast imaging modalities such as ultrasonography. Avoid angiotensin-converting enzyme (ACE) inhibitors and non-steroidal anti-inflammatory agents in volume depleted or otherwise susceptible patients. Cessation of drugs that may be causing interstitial nephritis e.g. penicillins should be considered as should the potential role for steroid therapy in this setting.

The prescription of drugs with nephrotoxic side effects is sometimes unavoidable in order to treat the primary disease process. Aminoglycosides, amphotericin and
vancomycin are widely prescribed in the ICU and are common causes of drug-induced AKI. Sustained elevations in aminoglycoside levels that occur from multiple daily doses seem to correlate with toxicity. Once daily administration of aminoglycosides in patients without pre-existing renal impairment is as effective as multiple daily dosing, is associated with a lower risk of nephrotoxicity and no greater risk of ototoxicity. Given the additional convenience and reduced cost, once daily dosing should be the preferred mode of administration.

In some circumstances the interval between administration of nephrotoxic agents e.g. aminoglycosides may need to be longer than one day for example in the presence of severe renal impairment. Trough levels guide the appropriate dosing interval.


AKI associated with conventional amphotericin B occurs in 25–30% of patients. The risk of AKI from amphotericin B increases with cumulative doses. There are several low powered studies to suggest that lipid formulations of amphotericin B result in less AKI. In one meta-analysis, involving over 9,000 patients, liposomal amphotericin B was found to be the least nephrotoxic (14.6%), when compared to conventional amphotericin B which was the most nephrotoxic (33.2%).


Q. What is the mechanism of the renal injury associated with amphotericin B and why is this ameliorated by liposomal preparations?

A. Amphotericin B is associated with afferent arteriolar vasoconstriction, reduced glomerular blood flow and direct cytotoxicity. The liposomal preparations have lower nephrotoxicity probably due in part to accumulation in the reticuloendothelial system rather than the kidney.

**Oliguria management algorithm**

The algorithm is for guidance only. It does not replace individualised clinical decision-making.
OLIGURIA

Resuscitate
Task 1

Clinical evaluation

Pre-renal oliguria

Evident hypovolaemia >55% patients
Task 2

Fluid challenge
Task 3

Response

no

Clinical re-evaluation.
Spot Na < 10
SG > 1018

yes

Repeat fluid challenge.
Examine for signs of CCF

Consider renal or post-renal oliguria

Evident heart failure
Task 2

Inotropy, inodilation
Specific therapies
Task 3

Response

no

yes

yes

no

Continue maintenance fluid. Consider further fluid challenges. Adjust for on-going losses.
Monitor

Consider concurrent diagnoses (sepsis, rhabdomyolysis, abdominal compartment syndrome) and specific therapy

Renal oliguria

Urine biochemistry & microscopy
Web appendix

yes

no

Specific therapy
Task 3

Post-renal oliguria

Ultrasound
Urine microscopy
Web appendix

Relief of obstruction
Specific therapy
Task 3
4. UNDERSTANDING OLIGURIA/AKI: AETIOLOGY, PATHOPHYSIOLOGY AND OUTCOME


Background physiology

Diet and the limitations of physiological adaptive capacity underlie the definitions of oliguria and anuria outlined in ‘Task 1’.

The normal osmolar production of an adult on a standard diet is approximately 600 mmol per day. Given that the maximum concentrating ability of urine is four times that of plasma i.e. 1200 mmol/l, it follows that a minimum of 500 ml of urine per day is required to excrete the normal daily osmolar load.

Physiological oliguria

Although rare in the intensive Care Unit and in the acute medical setting, oliguria may occasionally be physiological or can be anticipated as a feature of certain clinical states e.g. post surgery (especially cardiovascular) when ADH levels are high (Jochberger et al.) or of occasional therapeutic regimens/clinical management approaches. When a patient is being ‘run dry’ after thoracic surgery for example or when vasopressin (e.g. DDAVP for neurogenic diabetes insipidus) is being used therapeutically, oliguria can be anticipated and may not warrant intervention.


Careful clinical evaluation and confirmation of normal renal function by blood and urine biochemistry, particularly serum creatinine measurement, is required before attributing oliguria to a benign (physiological) cause.
‘Pre-renal’ oliguria – aetiology and pathophysiology

Circulatory dysfunction
This follows the general classification used for circulatory shock.

Hypovolaemic
Absolute e.g. severe blood loss, burns or diarrhoea
Relative e.g. anaphylaxis

Distributive
Septic, anaphylactic

Cardiogenic
Various aetiologies e.g. cardiac contusion and tamponade, myocardial ischaemia

Obstructive
Tension pneumothorax, pulmonary embolism

Cardiogenic shock is the extreme of the spectrum of cardiac failure. Cardiac failure may be absolute or relative – relative being when cardiac output (and consequently tissue oxygen delivery) are inadequate to meet augmented tissue demand e.g. in perioperative major surgery and trauma patients.

For further information about cardiogenic shock, see the PACT modules on Heart failure, Hypotension and Acute myocardial ischaemia

Other causes

Hepatorenal syndrome (HRS) is a potentially reversible form of renal failure that occurs in patients with cirrhosis and ascites as well as in patients with acute liver failure. In cirrhotic patients with ascites, pre-renal failure (42%) and acute tubular necrosis (ATN) (38%) represent the most common forms of acute kidney injury while HRS is somewhat less frequent (20%). HRS is characterised by marked renal vasoconstriction with a consequent reduction in renal plasma flow and glomerular filtration rate and the absence of pathological changes in the renal tissue. In patients with hepatorenal syndrome, systemic vasodilatation, in particular, splanchnic vasodilatation, is mediated via increased release of nitric oxide, carbon monoxide, glucagon, prostacyclin and adrenomelullin. This leads to an overall reduction in systemic arterial blood pressure and thereby activation renal vasoconstrictor pathways (the sympathetic nervous system, the renin-angiotensin system, and the non-osmotic release of vasopressin). It is the activation of these renal vasoconstrictor systems that in turn, are believed to induce functional AKI.

Accordingly, vasoconstrictors such as terlipressin may improve renal function by reducing splanchnic vasodilation and increasing central circulating blood volume and reducing endogenous renal vasoconstriction
Pre-renal oliguria may also be caused by direct renal artery compression or be associated with intra-abdominal hypertension. See Aetiology and Pathology of ‘Post-renal’ oliguria – Abdominal Compartment Syndrome.

**Pathophysiology**
The ‘pre-renal state’ – physiological response to circulatory dysfunction.

**Systemic response**

The general vascular response to tissue hypoperfusion or a reduced ‘effective’ vascular volume includes baroreceptor mediated sympatho-adrenal activation. Consequent venoconstriction and mobilisation of venous capacitance blood to the central circulation helps to preserve venous return, cardiac index and renal perfusion.

Sympatho-adrenal activity also stimulates resistance vessels, thereby increasing renal perfusion pressure; pre-capillary arteriolar vasoconstriction reduces capillary hydrostatic pressure and facilitates fluid resorption into the intravascular compartment from the interstitial space.

Conservation and expansion of ECF and intravascular volume is further favoured by thirst and ADH induced water retention. This is mediated primarily via venoatrial volume receptors and hypothalamic osmoreceptors.

‘Pre-renal’ oliguria is characterised by avid renal sodium and water retention which is physiologically designed to conserve intravascular volume, maintain cardiac index and preserve tissue (including renal) perfusion.

**Renal response**

Specific intrarenal, vasoregulatory, protective mechanisms designed to maintain glomerular filtration in response to reduced perfusion include:

- Afferent arteriolar myogenic (autoregulatory) vasodilation
Efferent arteriolar vasoconstriction via juxtaglomerular apparatus (JGA) induced renin-angiotensin mechanism

Intrarenal vasoregulatory change: prostaglandin induced diversion of blood flow to favour the juxtamedullary cortex

**NOTE** The kidney further contributes to the conservation of ECF and intravascular volume via renin-angiotensin induced aldosterone release and consequent sodium retention – effected primarily at the proximal tubular level.

An effect of these renal responses, in ‘pre-renal’ circumstances, is to favour the maintenance of the glomerular filtration rate (GFR) by increasing the filtration fraction i.e. the proportion of blood flow that is filtered. The favouring of juxtamedullary, cortical flow (see ‘renal response’ above) entails a reduction in medullary flow and thereby augmentation of the concentration gradient generated by the renal counter-current flow mechanism.

**NOTE** The mechanisms outlined promote sodium and water retention and enhance the concentrating effect on urinary urea and creatinine. The urine Na concentration falls (as a result of avid sodium retention) while the specific gravity and osmolality of urine rises, features which are useful diagnostically. See Task 2 and the appendix.
‘Renal’ oliguria – aetiology and pathophysiology

There is often significant overlap in the aetiology of oliguria.

Multifactorial renal insults are common. For example, in the patient with SIRS, factors such as hypotension, inadequate volume status, hypoperfusion and a disturbance of the balance of vasodilator and vasoconstrictor influences on the intrarenal microcirculation, may all contribute to oliguria. These changes may be exacerbated by iatrogenic insults such as aminoglycoside toxicity or the administration of radiographic contrast agents.

‘Renal’ oliguria may be classified under the following headings:

- Hypoperfusion/ischaemia
- Nephrotoxins
- Glomerular and vascular disorders
- Interstitial nephritis

**Aetiology**

**Ischaemia**
- Hypovolaemia/hypotension
- Sepsis (hypovolaemia, ischaemia, local neurohumoral response)
- Hepatorenal syndrome (including relative volume depletion)


**Toxins**

- Aminoglycosides, non-steroidal anti-inflammatory agents (analgesic abuse), radiocontrast media, amphotericin B, chemotherapeutic agents e.g. cisplatin
- Ethylene glycol, heavy metal poisoning, paraquat
- Pigment induced e.g. haemolysis and rhabdomyolysis

**Glomerular and vascular**

- Glomerulonephritis, thrombotic thrombocytopenic purpura (TTP), Haemolytic uraemic syndrome (HUS)
- Infective endocarditis
- Renal artery embolism, renal vein thrombosis, malignant hypertension
**Interstitial nephritis**

Drug induced e.g. penicillins, thiazides, frusemide, quinolones. Infection e.g. leptospirosis, streptococcal infection, Legionnaires’ disease.

**Q. What are the mechanisms of endocarditis-induced glomerular injury?**

A. In endocarditis, glomerular microvascular damage (glomerulonephritis) may be a consequence of direct antibody mediated toxicity e.g. anti-basement membrane antibodies or of indirect damage via immune complex disease.

**THINK** of how an understanding of aetiology may influence clinical practice. See examples in Task 3.

**THINK** of the possible mechanisms of renal injury in rhabdomyolysis and how they might be minimised by therapeutic intervention.

In addition to volume resuscitation and optimisation of renal perfusion, neutralisation of the acidic urine environment by alkalinisation may be achieved by administering intravenous sodium bicarbonate, titrated to achieve a urinary pH of ≥7.0. Acid urine favours the denaturisation and hence precipitation, of myoglobin and also the crystallisation of urate. Alkalinisation also inhibits myoglobin or haem induced lipid peroxidation. However, definitive clinical benefit of alkalinisation of urine has not been established.


‘Post-renal’ oliguria – aetiology and pathophysiology

Oliguria may be caused by obstruction occurring anywhere from the renal pelvis to the external urethral meatus. Obstruction may be intraluminal, in the wall or extrinsic to the urinary tract.

Renal dysfunction is mediated by increased intraluminal pressure as initially, glomerular filtration continues leading to distension of the ureter, renal pelvis and calyces. Despite the initial maintenance of renal blood flow, arteriolar vasoconstriction supervenes and GFR then falls. As is the case in many other causes of oliguria, activation of the renin-angiotensin system is contributory and may also be important in the subsequent generation of tubulointerstitial fibrosis.


**Intrinsic causes**

If a patient has a solitary kidney, either structurally or functionally, unilateral ureteric obstruction may result in acute renal failure

**Extrinsic causes**

A large retroperitoneal haematoma caused for example by overanticoagulation may cause extrinsic compression and deviation of the ureters

Cancer of pelvic viscera
Vascular aneurysm
Lymphoma
Retroperitoneal haematoma - anticoagulant therapy, trauma
Trauma (including iatrogenic ureteric injury)
Retroperitoneal fibrosis

Other causes – Intra-abdominal hypertension

Aetiology


Intra-abdominal hypertension (IAH) may complicate laparotomy and various pathologies. After repair of a ruptured abdominal aortic aneurysm, for example, intra-abdominal pressure may increase due to haematoma (often retroperitoneal) and extravasation of fluid into bowel, omentum and abdominal wall (‘third spacing’). Severe ascites, gastric distension or other causes of significant abdominal distension e.g. peritonitis or burns injury may also cause IAH. If intra-abdominal pressure approaches 20–25 mmHg, the complications of the abdominal compartment syndrome may arise. In these patients, other factors such as massive blood loss/massive transfusion and hypotension may contribute to oliguria.

The kidneys are especially vulnerable to IAH-induced dysfunction and AKI is one of the most consistently described organ dysfunctions associated with IAH. In critically ill patients, intra-abdominal hypertension is an independent predictive factor of AKI at intra-abdominal pressure levels as low as 12 mmHg.


Pathophysiology

Various pathophysiological mechanisms are associated with IAH.
Abdominal compartment syndrome results from elevated intra-abdominal pressure due to volume expansion within the confines of the abdominal cavity. Systemic haemodynamic compromise contributes to renal impairment and the high IAP may increase CVP spuriously, concealing hypovolaemia. However, as detailed by Biancofiore et al. (reference below), local compression of the renal parenchyma and veins appears to play a major role by reducing the renal filtration gradient. The renal response is activation of the renin-angiotensin-aldosterone system and upregulation of antidiuretic hormone. A profile consistent with acute tubular necrosis commonly follows relief of the abdominal compartment syndrome and is associated with both renal hypoperfusion and an oxygenated reperfusion injury. Direct ureteric compression does not appear to be important.


Outcomes after oliguria/AKI


Oliguria is a common problem in intensive care units and RIFLE and AKIN classification criteria of AKI (which incorporates the duration of oliguria) has facilitated a much better understanding of the epidemiology and outcomes of this condition. One- to two-thirds of ICU patients develop AKI according to these criteria, a complication that is associated with worse short-term outcomes such as increased length of ICU stay, costs, and mortality. Nearly half will be at increased risk of death because of AKI (as demonstrated in the three studies below). Unfortunately, current general clinical severity scores (APACHE, SOFA, etc.) are not good predictors of renal recovery but rather the severity grade of RIFLE and AKIN. To date, RIFLE criteria have been validated as outcome predictors in over 500,000 patients worldwide. A summary of mortality outcomes according to the RIFLE criteria is provided in Table 2.
Table 2

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Patient Number</th>
<th>RIFLE Outcome:</th>
<th>Risk</th>
<th>Injury</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joannidis et al</td>
<td>2009</td>
<td>14,356</td>
<td></td>
<td>29%</td>
<td>32%</td>
<td>43%</td>
</tr>
<tr>
<td>Bagshaw et al.</td>
<td>2008</td>
<td>120,123</td>
<td></td>
<td>17.9%</td>
<td>27.7%</td>
<td>33.2%</td>
</tr>
<tr>
<td>Ostermann et al</td>
<td>2007</td>
<td>41,972</td>
<td></td>
<td>20.9%</td>
<td>45.6%</td>
<td>56.8%</td>
</tr>
<tr>
<td>Uchino et al</td>
<td>2006</td>
<td>20,126</td>
<td></td>
<td>15.1%</td>
<td>29.2%</td>
<td>41.1%</td>
</tr>
<tr>
<td>Schneider et al</td>
<td>2010</td>
<td>3306 (pediatric)</td>
<td></td>
<td>18.9%</td>
<td>28.7%</td>
<td>42.5%</td>
</tr>
</tbody>
</table>


Ostermann M, Chang RW. Acute kidney injury in the intensive care unit according to RIFLE. Crit Care Med 2007; 35(8): 1837–1843; quiz 1852. PMID 17581483


Timely diagnosis of the aetiology and expeditious management are the main determinants of outcome. Recognition of oliguria allows the clinician to ameliorate these insults, for example by switching to an alternative non-nephrotoxic antibiotic or reducing the dose of, or stopping, diuretic when renal dysfunction is first recognised. Renal insults are heterogenous and some, such as rhabdomyolysis, may respond well to early resuscitation and treatment. If AKI supervenes, rhabdomyolytic ATN has a relatively better outcome. Other insults are less forgiving, renal failure in septic critically ill patients still being associated with a high mortality. Fortunately, several serum and urinary biomarkers will have an increasing role in the early diagnosis of AKI and hopefully will permit the clinician to intervene early to alter outcome.

For some e.g. high-risk patients requiring contrast studies, the opportunity to
provide prophylaxis arises and the prophylactic use of IV hydration with either sodium bicarbonate or normal saline and N-acetylcysteine may be helpful in minimising or preventing acute renal injury.

While short-term outcomes of critically ill patients surviving AKI has increasingly been documented, long-term, post-discharge information is lacking. It does seem, however, that for critically ill patients who develop AKI, (even those requiring RRT) but survive to hospital discharge the long-term outcome and quality of life is reasonable.


An incompletely answered question is the degree to which renal dysfunction persists after hospital discharge. In one study, renal dysfunction persisted in 41% of cases and 10% required maintenance dialysis. Many patients require transfer to a renal service to provide dialysis until recovery ensues. Frequently there is a pattern of reducing need for intermittent haemodialysis e.g. from three times to two times per week while renal recovery takes place. Occasional patients suffering very severe renal ischaemia develop acute cortical necrosis after which renal recovery is not anticipated although, anecdotally, this condition appears to be less common now.


As mentioned earlier, once AKI develops, mortality is high (40–60%) and survival figures are unchanged over the years, despite the availability of ‘improved’ methods of renal replacement therapy. Limited progress has been made in the field of treatments of AKI. Renal replacement therapy, at best, only provides partial renal support. Why, despite haemodialysis, does mortality remain high? Rodent AKI models do not resemble human renal injury and the absence of renal biopsy data limits our understanding of the pathophysiology of human AKI. In most cases, AKI develops as part of multiple organ dysfunction but AKI may lead to changes in distant organs including, brain, lungs, heart, liver, gasterointestinal tract, and bone
marrow. Acute lung injury (ALI) is currently the better characterised manifestation of distant organ injury secondary to AKI as inflammatory cytokines, in particular IL-6, play a role in the pathogenesis of ALI after AKI.

CONCLUSION

Oliguria/AKI is a serious and common complication in the critically ill. The increasing understanding of this syndrome has led to revised criteria for its definition and staging. A disparate range of conditions can cause oliguric AKI, including functional pre-renal states (the most common), obstructive conditions and a spectrum of intrinsic renal diseases including ATN, acute interstitial nephritis and glomerulonephritis. The aetiology is often multifactorial.

The diagnosis of a specific aetiology is usually based on careful assessment of history and physical examination aided by urinary diagnostic indices and microscopy together with renal ultrasonography. Fortunately, the development of several renal biomarkers is imminent to assist with the early diagnosis of AKI. The establishment of RIFLE/AKIN criteria to provide a standardised categorisation of the severity of AKI and the corresponding risk of death has assisted the acute/critical care management of kidney injury considerably. Early, active treatment of oliguria can avert AKI with the potential, thereby of greatly improving patient outcome.
5. **APPENDIX**

Urine analysis by the Medieval Itinerant Physician

ISBN 0671711326

**Urine reagent (‘Dipstick’) analysis**

Provides information on:
- Urinary pH
- Haemoglobin
- Myoglobin
- Protein
- Glucose
- Ketones
- Nitrites
- Leucocyte esterase
- Specific gravity

Although considerable discriminatory information can be gained from this simple test, caution is required in interpretation of dipstick results.

**pH**

Normal range 4.0 to 7.8.
An alkaline urine may be seen with infection with urea-splitting organisms, diuretic therapy and nasogastric suction.

**Haemoglobin**

Haemoglobin and myoglobin are detected by dipsticks. Haemoglobin has molecular weight of 65 kD and is poorly filtered, whereas myoglobin (17 kD) is readily filtered at the glomerulus.

False negatives may occur with high levels of ascorbic acid in the urinary tract. False positives occur with oxidising contaminants and povidone-iodine.
Absence of red blood cells on urine microscopy and positive dipstick for haemoglobin along with red or dark discoloration of the urine is consistent with intravascular haemolysis or rhabdomyolysis.

**Protein**
The physiological urinary protein excretion is 150 mg/day, including Tamm-Horsfall glycoprotein secreted by tubules and trace albumin of 15 mg/day. Cationic, low molecular weight proteins c. 20 kD are filtered at the glomerulus.

Nephrotic-range proteinuria of 3 g/day is usually glomerular in origin and 1-2 g/day tubular in origin.  
Selective glomerular proteinuria (with IgG/albumin ration of 0.1) is suggestive of minimal change glomerulonephritis.  
Early kidney transplant rejection is characterised by increased urine alpha2-microglobulin levels due to decreased tubular resorption of the filtered protein.

Proteinuria of <1g/day occurs in ATN.

Monoclonal gammopathies produce light chains that are filtered at the glomerulus to generate proteinuria of greater than 1g/day or Bence-Jones protein or a protein 'spike' on urine protein electrophoresis.

Interstitial nephritis due to non-steroidal anti-inflammatory drugs is occasionally accompanied by nephrotic-range proteinuria due to a concomitant minimal change lesion.

Microalbuminuria (or pauci-albuminuria) refers to urine albumin excretion of 30-300 mg/day that is not detected by dipstick examination and which is predictive of diabetic nephropathy.

Urinary reagent strips almost exclusively detect albuminuria at 250 mg/dl. Hence globulins e.g. Bence-Jones protein from monoclonal gammopathy will not be detected by dipstick techniques.

In the context of nephritic syndrome, a spot protein/creatinine ratio can increase the yield of detecting a glomerulonephritis.

**Glucose**
Renal threshold is 9–10 mmol/l (160-180 mg/dl) and the reagent strip will detect concentrations of 2.8 mmol/l (50 mg/dl).

**Ketones**
False positives may be obtained with sulphhydryl groups e.g. captopril.

**Leukocyte esterase**
Dipstick is sensitive for leucocytes even after lysis but is inhibited by mild glucosuria.
**Nitrites**
Bacteria convert nitrates to nitrites. False negatives may occur in alkaline urine.

**Biochemical analysis**

Urinary biochemical analysis comprises:
- Density
- Specific gravity
- Osmolality
- Tonicity
- Urine electrolyte concentrations

Specific gravity measurements are affected by glucose, protein, radiocontrast and mannitol.

Osmolality is a colligative property due to the number of particles in solution and is measured using depression of freezing point by an osmometer. Increased glucose concentrations may alter osmolality.

Reagent strip or ‘dipstick’ estimation of specific gravity is based on ionic strength and is affected by pH. ‘Dipstick’ method does not detect glucose-induced alterations in specific gravity. The normal range is 1.003 to 1.030.

**Urine electrolyte analysis**

‘Spot’ urine sodium

Sometimes considered ‘the poor man’s’ fractional sodium excretion but is nonetheless useful as an immediate supplementary measurement which is simpler to obtain.

Urine Na $< 10$ mmol/l = ‘PRE-RENAL’
Urine Na $> 40$ mmol/l = ‘RENAL’

A low urine sodium ($< 10$ mmol/l) reflects avid renal retention of sodium and corresponds with a low FeNa (see below). This finding suggests that oliguria is ‘pre-renal’.

A high urine sodium ($> 40$ mmol/l) corresponds with a high fractional excretion and suggests that oliguria is ‘renal’. Intermediate results are of uncertain significance.

**Fractional excretion of Sodium (FeNa)**

FeNa is a derived variable and relates sodium concentrating capacity to creatinine clearance. FeNa is a sensitive diagnostic index which differentiates pre-renal oliguria from renal impairment. FeNa is calculated from $\text{UNa} \times \text{PCr/PNa} \times \text{UCr} \times \text{FeNa}$

$\text{FeNa} < 0.01$ (<1%) = ‘PRE-RENAL’ (or a variation thereon – see below).
$\text{FeNa} > 0.02$ (2%) = ‘RENAL’ or ‘POST-RENAL’

Results falling between 0.01 (1%) and 0.02 (2%) are of indeterminate significance.

* The fraction is sometimes multiplied by 100 and expressed as a percentage.
A simpler ‘Renal Failure Index’ is sometimes used on the grounds that PNa does not change much and may therefore be excluded from the equation viz.

**BUN: Creatinine ratio:**

Using the units (mg/dL), the ratios quoted in the Task are derived and vary with the clinical circumstance.

[A conversion chart is included below if Urea and SI units are being used and a table of normal values is also included for reference]

The principle behind this ratio is the fact that both BUN (urea) and creatinine (Cr) are freely filtered by the glomerulus; however urea reabsorbed by the tubules can be regulated (increased or decreased) whereas creatinine reabsorption remains the same (minimal reabsorption).

The ratio may be used to determine the cause of the AKI (pre-renal versus ATN).

<table>
<thead>
<tr>
<th>BUN:Cr</th>
<th>Urea:Cr</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20:1</td>
<td>&gt;100:1</td>
<td>Pre-renal: BUN reabsorption is increased. BUN is disproportionately elevated relative to creatinine in serum</td>
</tr>
<tr>
<td>10–20:1</td>
<td>100–40:1</td>
<td>Normal Range</td>
</tr>
<tr>
<td>&lt;10:1</td>
<td>&lt;40:1</td>
<td>Intrinsic Renal Failure: renal damage causes reduced reabsorption of BUN, therefore lowering the BUN:Cr ratio</td>
</tr>
</tbody>
</table>

Normal serum values

<table>
<thead>
<tr>
<th>Test</th>
<th>SI units</th>
<th>US units</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN (Urea)</td>
<td>7–20 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>2.5–10.7 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>62–106 umol/L</td>
<td>0.7–1.2 mg/dL</td>
</tr>
</tbody>
</table>

**Urine sediment examination (microscopy)**

**Collection of urine sample**

The best sample is collected fresh by disconnecting the in-dwelling catheter from the collection bag a ‘clean catch’ sample. Do not obtain the sample from the urinary catheter bag. The specimen is transported in a sterile, transparent, dry plastic container without added disinfectant.

Urine sediment microscopy is not readily performed in the ICU as it requires centrifugation and microscopy. Fresh urine should be spun by centrifuge and the sediment examined microscopically by trained personnel within an hour of
collection. It should not be relegated to batches in the laboratory where examination may be delayed. A nephrology service, when available, can be expected to provide this service expertly and consistently.

Patterns indicative of ATN, glomerulonephritis and interstitial nephritis may be evident.

**Formed elements**

**Red blood cells**

A positive dipstick test for haematuria should be followed by urine microscopy for red blood cells. Absence of red blood cells indicates the presence of haemoglobin or myoglobin in the urine. Dysmorphic RBCs are usually glomerular in origin. Normal urine may contain 5 RBCs and 3 WBCs per high-power field.

Abnormal numbers of red blood cells may be present in:
- Glomerulonephritis
- Renal thrombosis
- Ureteric colic

**White blood cells**

The presence of more than 1-3 WBC per high-power field is abnormal. Usually leukocytes in the urine are polymorphonuclear neutrophils. Eosinophiluria is typically associated with allergic interstitial nephritis, or with urinary tract infection. Atheroembolic renal failure presents with eosinophiluria, hypocomplementaemia and livedo reticularis.

**Other cells**

Renal tubular cells, bladder urothelial cells and urethral squamous cells may also be found in the urine.

**Lipids**

Lipid may be present in urine in droplet form (oval fat bodies) or as crystals. Lipid droplets are translucent and when they contain cholesterol, have a ‘Maltese cross’ appearance in polarised light. Lipiduria is found in heavy proteinuria or nephrotic syndrome but may also be found in fat embolism syndrome.

**Casts**

Casts are elongated cylindrical formed elements which originate in the distal tubules or collecting ducts from a matrix of Tamm-Horsfall protein. Hyaline casts contain Tamm-Horsfall protein and are considered non-pathologic.

They may be present in heart failure or fever without renal dysfunction. Decreased urine volume and acid urine favour cast formation.

Granular casts are considered pathologic (Image 1). Sloughed tubular cells form a dark, granular cast, the ‘muddy brown’ cast of acute tubular necrosis.
Cellular casts consist of epithelial cells, red blood cells or white blood cells. Red blood cell casts (Image 2) occur in glomerulonephritis.

White blood cell casts (Image 3) are found in pyelonephritis, interstitial nephritis and glomerulonephritis.

Tubular epithelial cell casts occur in nephritic or nephrotic syndrome. Fatty casts (Image 4) may occur in nephrotic syndrome and heavy proteinuria.
Waxy casts (degenerated cellular casts) are seen in chronic renal disease, as are broad granular casts. Pigmented casts may be haemoglobin casts, which occur in intravascular haemolysis, or myoglobin casts, which occur in rhabdomyolysis.

**Crystals**
Crystal precipitation may occur with changes in temperature and pH and is non-pathologic. Alkaline urine contains phosphate crystals. Acid urine contains uric acid, oxalate, amino acids (cysteine etc) or cholesterol crystals. Uric acid crystals (Image 5) are amber and birefringent in polarised light.

Crytalluria is found in association with:
- Acute urate nephropathy
- Methotrexate
- Sulphonamides
- Acyclovir
- Rhabdomyolysis
- Ethylene glycol toxicity (oxalate and hippurate)

**Bedside diagnostic renal ultrasonography**

**Basic principles**
The sonogram image is a digital tomogram with each picture element (pixel) assigned a light intensity (grey shade) proportional to the intensity of the reflected sound beam. Structural features assessed on renal sonogram are size, echogenicity, corticomedullary differentiation, pelvicalyceal system size and other morphological abnormalities.
Obstruction to the collecting system caused, for example by prostatic hypertrophy may be evident. Renal pathology such as a tumour may also be diagnosed. Congenital renal anomalies may be identified e.g. renal agenesis, horseshoe kidney, duplex ureter, supernumerary kidney or pelvic kidney.

Colour Doppler allows assessment of vessel patency and blood flow velocity in renal artery and vein in both native kidneys and allografts. Renal arterial and venous thrombosis, renal artery stenosis, AV fistulae and pseudoaneurysms may be seen. It also provides information on kidney size, enlarged kidneys being typical for AKI but small kidney(s) for chronic kidney disease. Papillary necrosis can be detected and might be useful in the diagnosis of analgesic nephropathy. Duplex sonography may distinguish between intrinsic and pre-renal disease.


**Hydronephrosis**

Normal calibre pelvicalyceal system and ureters does not rule out obstructive uropathy. With extrinsic compression (retroperitoneal fibrosis), ureteric calibre may be within normal limits.

**Pyelonephritis**

May cause diffuse renal enlargement with increased echogenicity due to the inflammatory infiltrate. Intrarenal abscesses appear cystic with some low-level echogenic areas consistent with pus. Gas-producing organisms in association with emphysematous cystitis may produce areas of acoustic shadowing. Extension of infection may produce a perinephric abscess or a pararenal collection.

**Kidney transplant evaluation**

Ultrasound evaluation of the graft in the acute rejection phase will show loss of corticomedullary differentiation and small fluid collections in the renal pelvis. Spectral Doppler analysis of flow in the graft artery and adjacent external iliac artery will show increased resistance (resistivity index) in acute rejection. This finding is sensitive but not specific. Such findings are helpful in differentiating rejection from immunosuppressive agent toxicity.

**Renovascular disease**

In atheromatous disease, atheroma may be visible at the renal ostium. In renal artery stenosis characteristic spectral Doppler flows are present. Renal vein thrombosis, a complication of nephrotic syndrome, has ultrasound appearances of increased renal vein size containing clot with perinephric fluid collection.

Links to ‘Bedside ultrasonography’ in the appendix (Task 5).
SELF-ASSESSMENT QUESTIONS

EDIC-style Type K

1. The first stage of acute kidney injury (AKI) risk categorisation includes:
   A. Urine flow less than 0.5 ml/kg/hr for an hour
   B. Urine flow less than 0.5 ml/kg/hr for two hours
   C. Urine flow less than 0.5 ml/kg/hr for six hours
   D. Urine flow less than 100 ml for 12 hours

2. In most oliguric patients the cause is
   A. Renal
   B. Post-renal
   C. Pre-renal
   D. Equally distributed

3. Uraemia is:
   A. A clinical syndrome with encephalopathy, bleeding and pericarditis
   B. The elevation of serum urea
   C. Acute kidney injury with oliguria
   D. Anaemia in chronic renal failure

4. Acute kidney injury is associated with
   A. Hyperkalaemia
   B. Alkalosis
   C. Hyperphosphatemia
   D. Hypocalcaemia

5. In a patient with suspected acute kidney injury the purpose of ultrasonography for diagnostic work-up is
   A. To rule out obstructive causes of oliguria
   B. To measure glomerular filtration rate (GFR)
   C. To detect kidney size
   D. To estimate blood flow to the kidney

6. Vasopressors are sometimes used in patients with acute kidney injury (AKI). Which statement(s) of various vasoactive drugs is/are true?
   A. Epinephrine may induce an increase in lactate production
   B. Dopamine may increase urine output
   C. Norepinephrine may improve survival compared to dopamine
   D. Vasopressin is contraindicated in all forms of AKI

7. Epidemiology of Acute Kidney Injury (AKI) in the critically ill patient population shows that:
   A. Approximately 1:10 develops AKI
   B. The mortality does not increase when going from Risk to Failure in the RIFLE criteria
   C. The ICU length of stay increases in patients with AKI compared to non-AKI patients
   D. In the failure group more than 50% of the patients die in the hospital
EDIC-style Type A

8. In patients with suspected pre-renal oliguria a fluid challenge is often given. Which of the following fluid challenge regimens is INCORRECT?
   A. 10–15 ml/kg of Ringer’s Lactate
   B. 5 ml/kg albumin 40 mg/ml (4%)
   C. 25 ml/kg glucose 50 mg/ml (5%)
   D. 15 ml/kg of mannitol 20%
   E. 10–15 ml/kg of saline (NaCl 9 mg/ml)

9. Which of the solutions have been claimed to increase the risk of acute renal failure in patients with sepsis?
   A. Ringer’s lactate
   B. Hydroxyethyl starch
   C. Albumin 200 mg/ml (20%)
   D. Dextran 70
   E. Tris buffer (THAM)

10. The most common cause of post-renal oliguria in the ICU is:
    A. Prostatism
    B. Bladder haematoma
    C. Retroperitoneal bleeding
    D. Blocked urinary catheter
    E. Urinary bladder infection

11. According to the AKIN criteria, the diagnosis of acute kidney failure is based on:
    A. An elevation of serum creatinine or serum urea
    B. An elevation of serum creatinine or oliguria
    C. A reduction in glomerular filtration rate
    D. A 3-fold elevation of serum creatinine and anuria for 12hrs
    E. Urine–creatinine ratio <20

12. All of the following procedures may reduce the risk of developing acute kidney injury, EXCEPT:
    A. Avoid ACE inhibitors
    B. Use of non-ionic contrast agent
    C. Avoid aminoglycosides
    D. Avoid liposomal amphotericin B
    E. Avoid non-steroidal anti-inflammatory drugs (NSAIDS)

13. In normal kidneys, what is the minimum urine volume in order to excrete the normal daily osmolar load?
    A. 250 ml urine
    B. 500 ml urine
    C. 750 ml urine
    D. 1000 ml urine
    E. 1500 ml urine
**Self-assessment answers**

**Type K**

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**Type A**

8. Answer D is correct
9. Answer B is correct
10. Answer D is correct
11. Answer D is correct
12. Answer D is correct
13. Answer B is correct
PATIENT CHALLENGES

A 62-year-old female, Mrs P. presents with severe shortness of breath at rest and chest pain, progressively worse over the past 24 hr. She is known to have a history of congestive heart failure (left ventricular ejection fraction is 25%), ischaemic cardiomyopathy and type 2 diabetes mellitus. She has had two hospitalisations for acute decompensated heart failure in the past 12 months. Her outpatient medications include an ACE inhibitor, beta-blocker, aldosterone antagonist, frusemide and gliclazide. On admission she was noted to have severely altered mentation with a glascow coma scale of 8, pulse rate of 104/min, sinus rhythm, BP 80/60mmHg, CVP 19 mmHg, oxygen saturation of <87%. Examination and chest X-ray reveal evidence of volume overload with pulmonary odema. She had evidence of acute coronary syndrome with ischaemic changes on ECG. The patient was intubated and ventilated (low GCS and cardiogenic shock) and a dobutamine infusion of 10 µg/kg/min was commenced but noradrenaline was at hand in case hypotension occurred. She was transferred to the heart catheterisation laboratory, where no percutaneous coronary intervention was required but a right heart (pulmonary artery) catheter (PAC) was placed by the cardiologist.

Q. Would you consider this patient to have a low or high risk of developing AKI during her hospitalisation with acute decompensated heart failure (ADHF)?

A. Approximately 30% of patients admitted with ADHF develop worsening renal function. This risk is higher in patients with prior chronic kidney disease. The development of AKI is associated with worse clinical outcomes.

Learning issues

Risk of AKI

Q. How would you manage volume overload in this patient?

A. Once blood pressure is stabilised and if oliguria persists despite the titrated dobutamine infusion, intravenous frusemide could be given, e.g 80mg three times daily or by continuous infusion of 10–20mg/hourly. Alternatively, in diuretic resistant cases extracorporeal ultrafiltration may be considered.

Learning issues

Indication for diuresis (frusemide)

Q. Assuming she is aggressively diuresed, how would you define a case of AKI? How would you monitor the patient for evidence of developing AKI?

A. AKI is defined according to the current AKI classification systems, AKIN and RIFLE. Assessment of the patient for a developing AKI is by measurement of serum creatinine (and urea) q12hrly for evidence of rising values. A urinary catheter should be inserted and urinary output monitored hourly (including diuretic responsiveness).
AKI classification

Her creatinine was found to be 270 µmol/L (3.05 mg/dL) and she had a baseline creatinine of 130 µmol/L. A urinary catheter was passed and was draining <20ml urine hr the past 12 hours.

Q. What severity of AKI by either RIFLE or AKIN does she have and what does categorisation achieve?

A. Mrs P. would be classified as ‘I’ in RIFLE and stage II AKIN. Categorisation facilitates rational clinical management and can predict clinical outcomes. She may have more than three times the mortality rate of patients without AKI, with an odds ratio of hospital mortality of 2.54.

Classification of AKIN/RIFLE systems (Table 1)


Q. What should be the response to this patient’s decline in urinary output?

A. Ensure an initial assessment of urinary catheter position and patency:
   Exclude urinary obstruction
   Search for the cause(s), including drugs and remove or treat.
   Optimise cardiac output and blood pressure
   Avoid volume loading given severe LV dysfunction.
   Commence initial work-up with renal ultrasonography, urine chemistries and microscopy/analysis.
   Monitor for complications of AKI
**Response to oliguria**

*Ensuring an adequate volume status in oliguria*

?urine dipstick

**Q.** List the factors that are likely contributors to oliguria and possible AKI in this patient.

**A.** Hypotension, ADHF with poor renal perfusion, nephrotoxic drugs including ACE inhibitors and diuretics, pre-existing CKD, (‘cath lab’) contrast nephropathy.

**Q.** Now that AKI has developed, how would you distinguish between pre-renal azotaemia and acute tubular necrosis?

**A.** Urine dipstick, urine chemistries, urinalysis/microscopy and urine NGAL.

Biochemical evaluation of urine in this case demonstrates pre-renal azotaemia: SG is 1.020, ‘spot’ urine sodium is 4mmol/L and FeNa iso.6. Her urine NGAL measured 746 ng/ml (normal range 0.7–9.6 ng/mL). Limited evidence suggests a single emergency department urinary NGAL level was highly predictive of AKI and predicts poor patient outcomes.

**Learning Issues**

*Identifying pre-renal oliguria*


**Q.** There appears to have been a good haemodynamic response to dobutamine (BP 110/65, HR 105, CVP 14, peripheral perfusion, ScvO2 and lactate improved) but the oliguria persists. How do you ensure the patient’s volume status is adequate?

**A.** An echocardiogram would provide an accurate assessment of the patient’s volume status (LVEDV) and cardiac function. The use of the already placed pulmonary artery catheter (PAC) might be reasonable, although evidence in favour of the use of these devices is conflicting.
Treatment of oliguria

The cardiac index is 2.6 l/min/m², the PAOP 16 mmHg and the SvO₂ is 50%.

Q. How do you interpret these findings in this circumstance?

A. The low/normal cardiac index and the low SvO₂ together with the clinical circumstances indicate that cardiac output is inadequate. The high PAOP indicates a concurrent congestive component to the cardiac failure. You decide to increase the dose of dobutamine.

Haemodynamic evaluation of pre-renal oliguria

Your colleague who is involved in the management of this patient has suggested that ‘renal dopamine’ would be particularly appropriate at this juncture. He is of the opinion that dopamine improves renal blood flow in experimental conditions and should be employed here. Although he is aware that there is controversy about the drug, he feels that dopamine in ‘renal’ or ‘low’ dose (1–3 mcg/kg/min) will do little harm. You are aware of the evidence with regard to ‘renal dopamine’ in human patients and mention that there has been no renal benefit demonstrated.

Q. Do you agree however that low-dose dopamine ‘cannot do much harm’? Explain your answer?

A. No. Its use will contribute to unnecessary polypharmacy and may predispose to a variety of complications such as arrhythmia and hypoxemia. There is also suggestive evidence that it causes confusion in ICU patients. In the long term, pituitary suppression may become a problem. Several meta-analyses have concluded that ‘renal dose’ dopamine is of no benefit in either preventing or ameliorating AKI in the critically ill and may even promote AKI. In addition, low-dose dopamine may also interfere with the hypothalamic-thyroid glands.

Lack of efficacy of ‘renal dose’ dopamine

You decide against dopamine and instead increase the dose of dobutamine, which results in an increased cardiac index. Mrs P’s urinary output returns to 60 ml/hr after 24–36 hr and her renal function settles to baseline after 3–4 days.

At day 9, Mrs P is recovering from her renal and cardiac failure and is being weaned from her adrenergic drugs. Mrs P complains of abdominal and lower extremity muscle pains. Her serum creatinine increases to 220 µmol/L and her urinary output is now 10–15ml/hr. Her amylase is elevated at 320 U/L, with a creatinine phosphokinase of 470 IU/mL. Her urine specific gravity is 1.012, with 1+ blood and 2+ proteinuria by dipstick. Microscopic examination reveals 3 to 5 red blood cells per high-power field, rare white blood cells, and a moderate number of fine granular casts.

Evolving skin changes after coronary angiography – picture taken at day 9.

Q. What is the most likely cause of the patient’s recurrence of AKI?

A. The diagnosis is most likely atheroembolic disease as suggested by the delayed development of AKI after an angiographic procedure, accompanied by symptoms of systemic atheroembolisation. The lower extremity muscle pains and elevated creatine kinase reflect muscle involvement; the abdominal pain and elevated serum amylase reflect pancreatic and/or intestinal embolisation; the raised creatinine may indicate embolisation to the renal arteries.

Athero-embolic disease as a cause of AKI
A diagnosis of contrast nephropathy is unlikely given the late (>48hrs) onset of AKI after contrast administration.

Rhabdomyolysis must be considered in view of the muscle pain and dipstick positive urine. However, there is no acute hyperkalaemia or other biochemical markers of this diagnosis. The absence of pigmented casts in the urinary sediment with only a mild elevation of creatinine kinase also goes against rhabdomyolysis.

A diagnosis of pre-renal azotaemia is less likely given the presence of isothenuric urine (manifested by the specific gravity of 1.012).

On clinical examination of her foot, embolic manifestations have become evident (see figure). In addition, her right calf, which had been ‘doughy’ has now become tense and swollen and increasingly tender despite i.v. opioid analgesia. The dorsalis pedis and posterior tibial pulses are absent both to palpation and on Doppler ultrasonography.

You measure muscle compartment pressure and find it to be 30 mmHg. Your colleague reminds you that clinical examination is of primary value in assessment of ischaemia but accepts that measurement of compartment pressure is often helpful diagnostically.

Fasciotomy is discussed but capillary refill of the toes and foot, along with a Doppler signal of the posterior tibial artery improve. However, the patient remains oliguric and later biochemical testing reveals a further elevation in CPK to 15,200 IU/ml. The serum potassium is now 6.5mmol/L (quite acutely) and hyperphosphataemia and hypocalcaemia are evident. Urinary testing reveals myoglobinuria.

Quality of clinical outcome for this patient depends on both limb salvage and overall survival. One large review noted a substantial increase in mortality (59.6%), in patients who suffered ischaemic vascular complications e.g. with an intra-aortic balloon pump (IABP) and an amputation rate of 3.4%.

Q. Why might the patient be deteriorating despite an improvement in clinical perfusion?

A. The clinical scenario, the hyperacute rise in serum potassium and the other biochemical abnormalities now suggest a rhabdomyolytic syndrome.

**Note**

Rhabdomyolysis as a cause of AKI

Q. Explain the biochemical abnormalities of rhabdomyolysis?

A. Release of intracellular electrolytes from the ischaemic muscles with hyocalcaemia resulting from the acute rise in serum phosphate.
Oliguria persists despite cardiovascular optimisation bearing in mind this patient’s poor myocardial reserve. A urinary pH of 5.0 is noted by the intensive care nurse who wants to know if the aciduria is to be corrected.

**Learning Issues**

Pathophysiology of rhabdomyolytic oliguria

**Q.** How does an acid urine exacerbate the pathology?

**A.** A variety of factors including renal vasoconstriction and hyperuricaemia are involved but the tubular toxicity of myoglobin and lipid peroxidation is theoretically aggravated by an acid urine.

The acute rise in serum potassium (K+ 5.5 to 6.8 mmol/l) represents a life-threatening progression and occurred despite the therapies already instituted which include volume expansion, administration of bicarbonate, insulin/dextrose infusion and efforts to promote a kaliuresis.

**Learning Issues**

Manipulation of urine pH (alkalinisation) in oliguria

**Q.** What therapy is required now?

**A.** Dialytic therapy is indicated given the failure of the above measures to control hyperkalaemia.

**Learning Issues**

Indications for dialytic therapy in AKI

Following institution of continuous haemodiafiltration, the biochemical abnormalities in this patient were more easily managed. With increasing haemodynamic stability over the next week, she was changed to intermittent haemodialysis. Following transfer to the high dependency unit, she required intermittent dialysis three times weekly for three weeks while renal function recovered. There was a short polyuric phase during renal recovery; dialysis frequency decreased and stopped after another two weeks. Following a further two weeks in a convalescent centre, she was discharged home, feeling well, on cardiac medications at ten weeks post surgery. She was scheduled for review in the renal clinic.
A 51-yr old man, Mr. L is admitted to ICU with severe abdominal pain of two weeks duration. He has no past medical history except for epilepsy for which he takes sodium valproate. His BP is 95/60mmHg, pulse rate of 120 bpm (sinus rhythm) and he is pyrexial at 38.4°C. Physical examination is remarkable for abdominal distention and tenderness, his serum amylase and lipase are elevated. A urinary catheter is placed and although his urine output was previously 50ml/hr it has now decreased to 15–25ml/hr since his CT abdomen and pelvis was performed over 24hrs ago. The CT abdomen and pelvis demonstrates extensive pancreatic oedema, a significant amount of intraperitoneal ascites and small number of intra-abdominal collections. His white cell count (WCC) is 20 x 10^9/ul and his creatinine is 212 µmol/l. A diagnosis of necrotising pancreatitis is made.

**Learning Issues**

Pancreatitits as a cause of AKI

**Q. What is the aetiology of Mr. L’s oliguria?**

**A.** Pre-renal azotaemia, intrinsic AKI including ATN and sepsis, nephrotoxic antibiotic use, contrast-induced nephropathy and intra-abdominal hypertension (IAH) from abdominal compartment syndrome (ACS) must all be considered here.

**Learning Issues**

Aetiological factors in pancreatitis-related AKI

**Q. Diuretic therapy is controversial for oliguria; do you agree with its use here? When might you use frusemide?**

**A.** Oliguria per se is not an indication for frusemide. However, frusemide may be required for volume control in oliguric patients with pulmonary oedema and hypervolaemia. Hyperkalaemia is another indication

**Learning Issues**

Indications for frusemide

**Q. If frusemide achieves a diuresis for Mr L, will this improve his renal outcome?**

**A.** No. Neither a reduction in the need for dialysis, or in its duration, has been shown.

**Learning Issues**

Lack of efficacy of frusemide in AKI
Ho KM, Sheridan DJ. Meta-analysis of frusemide to prevent or treat acute renal failure. BMJ 2006; 333(7565): 420. PMID 16861256


Q. Are there important side effects to frusemide deployment here?

A. Hypovolaemia (and aggravation of pre-renal AKI) is the most immediate potential problem together with observational evidence associating frusemide with a worse renal outcome. Renal insufficiency, hypernatraemia, metabolic alkalosis, interstitial nephritis and ototoxicity (associated with high dose frusemide) are other recognised adverse effects of frusemide.

**Learning Issues**

**Side effect of frusemide**

Q. What are the initial management imperatives to restore urinary output?

A. Restoration of the circulation. This will initially consist of fluid replacement to compensate for the expected large volume losses into the abdomen. The addition of an inotrope and/or vasopressor will be dependent upon the response to fluid. Mr. L. is volume-resuscitated with approximately 8L of crystalloid, and his BP improves to 135/85 mmHg. If sepsis is suspected, cultures are done and broad-spectrum antibiotics (renal doses) are given – prophylactic antibiotics are not recommended.

**Learning Issues**

*Initial approach to oliguria*

*Link to Pancreatitis module*

**Note** If the abdomen is distended, consider measurement of intravesical pressure using an in-dwelling urinary catheter water manometer or a pressure transducer as a reflection of intra-abdominal pressure.

**Learning Issues**

*Intra-abdominal hypertension*
**Q.** Mr. L’s intra-abdominal pressure is 30–32 mmHg for two readings. Does he have IAH or ACS?

**A.** IAH is defined as sustained or repeated pathologic elevation of the intra-abdominal pressure (IAP) above 12 mmHg and ACS is the sustained elevation of IAP above 20 mmHg in combination with newly developed organ dysfunction. Given that he has developed AKI, he has ACS as a complication of his IAH.

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**Learning Issues**

**Measurement of intra-abdominal pressure**

*Link to ACS in module on Intra-abdominal problems*

**Q.** What are the treatment options for IAH and ACS in our patient?

**A.** Non-surgical measures to reduce IAP should be undertaken first, and if ineffective, consider surgical approaches in patients with persistent organ dysfunction. Strategies aimed at reducing IAP include: nasogastric suction, colonic decompression, percutaneous intra-abdominal abscess drainage or wide-bore tube (or other) image-guided drainage of necrotic pancreatic tissue.

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**Learning Issues**

**Treatment of IAH/ACS**

In patients with large volumes of pancreatic ascites, percutaneous drainage of the intraperitoneal exudates can lead to a significant drop in IAP. The use of neuromuscular blockers and in one study the use of continuous venovenous haemodiafiltration (CVVHDF) has been described. However the use of CVVHDF for the treatment of IAH remains to be validated in large prospective studies. Surgical measures to reduce IAP include decompressive laparotomy. Because of the significant morbidity associated with surgical decompression and the management of the ensuing open abdomen, more research is needed to better define the appropriate indications and techniques for surgical intervention.


PACT module on Pancreatitis
A 68-year-old, hypertensive, male, with a recurrence of angina pectoris which persisted despite medical therapy, underwent revision coronary artery bypass grafting. Pre-operative echocardiography revealed a left ventricular ejection fraction of 35%. He becomes oliguric four hours post operatively. Heart rate is 105/min (SR), BP 100/70 mmHg, CVP 7mmHg and lactate is 4mmol/L.

**Learning Issues**

*Lactate as an index of decreased survival*

**Q.** What is your initial management?

**A.** You decide to volume load as a ‘fluid challenge’ using 10–15 ml/kg of crystalloid and then you repeat with a colloid solution. After these two challenges, the BP, CVP and resuscitation endpoints, other than persisting oliguria, become satisfactory.

**Learning Issues**

*Initial response to managing the oliguric patient*  
*Volume loading therapy in oliguric/AKI patients*

Regarding the cause of the oliguria, a review of the notes and history from referring anaesthesia/surgical teams show that although anaesthesia was generally uneventful, a pre-operative pulmonary artery catheter had been placed to guide therapy given his higher risk status. Surgical revascularisation was satisfactory but hypotension, due to apparent myocardial stunning, at the time of weaning from cardiopulmonary bypass (CPB) necessitated high dose inotropic therapy and placement of an IABP. Perioperative antibiotic prophylaxis was with vancomycin and gentamicin as there was a history of penicillin allergy.

**Learning Issues**

*Diagnosis of cause of AKI – clinical including drug history*

**Q.** List the factors that are likely contributors to oliguria and possible AKI at this time.

**A.** Hypotension, acute decompensated heart failure, nephrotoxic drugs and CPB status.

**Learning Issues**

Link to *PACT module on Heart failure*

Initial i.v. volume resuscitation to a PAOP of 15 mmHg together with an increase in inotrope therapy (dobutamine 15 µg/kg/min), achieved an improvement in the cardiac index (2.2 to 2.6 l/min/m2) and in SvO₂ from 55 to 65%. Blood lactate has fallen from 5 (at peak) to 3mmol/L. However the patient remains oliguric (20–30mls/hr). There is bedside debate as to whether the patient could still be ‘pre-renal’ despite the
haemodynamic improvement with presumed corresponding improved renal perfusion. A urine dipstick test for specific gravity (and other pointers to pathology) and urine biochemistry to analyse renal concentrating capacity show a pre-renal pattern – urine SG is 1.020, ‘spot’ urine sodium is 8 mmol/l and FeNa is 0.5. These findings are interpreted as indicating further measures to reverse the pre-renal state.

You perform a leg elevation manoeuvre with some apparent responsiveness but a further trial of fluid therapy does not improve the oliguria.

**Learning Issues**

*Physical examination of the oliguric/AKI patient*

*Haemodynamic optimisation for oliguria/AKI.*

*Link to PACT module on Haemodynamic monitoring.*

Although there has been haemodynamic improvement and the patient is well volume loaded (filling pressures in the 12–16 mmHg range and no further response to fluid). The MAP is 70 mmHg. Given the patient’s background of hypertension, a trial of BP augmentation is initiated using a noradrenaline (norepinephrine) infusion in an initial dose of 0.05–0.5 mcg/kg/min. The dose is titrated to a mean arterial pressure of 85–95 mmHg resulting in an improved urine flow (50–60/hr). Dobutamine is also commenced to maintain improve cardiac output and perhaps facilitate weaning of the IABP. Monitoring for excessive vasoconstriction is done clinically and by serial lactate measurement.

**Learning Issues**

*Inotropic/vasopressor infusion in oliguria*

The patient appeared to stabilise initially with an apparently trivial associated rise in serum creatinine (116 to 150 µmol/L). On day two however, he remained oliguric (<30 ml/hr) with a rising creatinine (232 µmol/L-double his admission value). His CVP/PAOP were 9/12 mmHg, mean arterial pressure was 80 mmHg and dobutamine/noradrenaline continued at moderate doses.

Despite haemodynamic improvement and volume loading the patient remains oliguric with worsening renal indices. You reassess for an alternative cause for the AKI. The patient had not received any nephrotoxic agents or antibiotics since surgery. You decide to order a bedside renal ultrasound to exclude obstructive uropathy. You dipstick the urine and order a repeat urine chemistry. There is no evidence of sepsis. You consider that cardiopulmonary bypass may be the cause of the AKI.

**Learning Issues**

*Urine testing for aetiology of oliguria/AKI*

*Urine dipstick exam in oliguria*

*Fluid responsiveness in oliguric/AKI patient*

*Ensuring an adequate volume status in oliguria*

*Renal autoregulation in hypertension*
Noradrenaline (vasoconstrictor) therapy to increase MAP for oliguria/AKI.

Q. What is the pathophysiological basis for the development of AKI post cardiopulmonary bypass (CPB)?

A. AKI is an important complication of cardiac surgery/CPB that affects 30–50% of patients, 5% require renal replacement therapy (RRT). Risk factors for development of AKI associated with CPB include: reduced renal perfusion during CPB, increasing age, diabetes, presence of pre-existing CKD, and increasing length of time on CPB (longer for re-do CABG and valve repairs).

Haemolysis is a common consequence of CPB that is caused by mechanical damage in the perfusion circuit/pump and results in the release of haemoglobin from lysed erythrocytes. Although several mechanisms of CPB-associated AKI have been proposed, free serum haemoglobin may be a major contributor. Furthermore, CPB-associated AKI may be a form of pigment nephropathy where in an acidic environment, the conversion of haemoglobin to met-haemoglobin forming casts is thought to be an important pathophysiological step.

**Learning Issues**

Serial haemodynamic adjustment to treat oliguria


**Learning Issues**

CPB as cause of AKI

The renal ultrasound confirms normal sized kidneys bilaterally with no evidence of hydronephrosis. Urine SG is 1.020, ‘spot’ urine sodium is 6 mmol/l and FeNa is 0.4 and thus reflects avid sodium retention in response to a pre-renal status.

Q. Why, despite adequate volume loading with haemodynamic improvements, does the urinalysis reveal a pre-renal profile of AKI? What IABP-related cause might there for the patients AKI?

A. A possible cause of the pre-renal failure is the intra-aortic balloon pump (IABP) causing compression of the renal arteries.
Renal USS in AKI

Q. Give arguments as to why you would remove the IABP?

A. Likely improvement in renal perfusion but benefit may be offset by the anticipated fall in cardiac output.

The position of the tip of the IABP was checked on a plain film X-ray and was probably impairing renal perfusion. The IABP is removed and urinary output returns to 50ml/hr over the following 12 hours. Creatinine returns to baseline over the next 3 days. Following a further two weeks in hospital, he was discharged home, feeling well. The only complication of his postoperative course was AKI resulting in prolonged ICU and hospital stay. He is scheduled for review at renal outpatient clinic.

On reflection,
Most instances of oliguria are ‘pre-renal’ in nature but still require individual assessment and targeted therapy. The ‘pre-renal’ state needs confirmation and there is a need for universal appreciation of the level of risk (to survival) involved in all levels of AKI – even at the lower (‘risk’) of the AKI categorisation. Volume loading and treatment of cardiac failure/circulatory dysfunction is the key to successful management. The most common risk for AKI among the critically ill is sepsis and, like all causes of AKI including rhabdomyolysis, it requires prompt specific therapy.

Circulatory support using fluid and vasoactive therapy to improve renal perfusion is often indicated. Dopamine in ‘renal dose’ or frusemide therapy, although widely used until recently, have no ‘renoprotective’ role in human critically ill patients. Occasionally, there is the opportunity to prevent AKI by prophylactic therapy e.g. N-acetylcysteine or bicarbonate before contrast administration or CPB. Failure to avert ARF by prophylaxis or by targeted treatment of septic or other underlying causes is associated with increased mortality and, even in those who do survive, the risk of long-term dialysis dependence is higher than hitherto appreciated.