Acute Kidney Injury (AKI) – A Global Problem

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Chronic renal failure is familiar to all doctors. The condition ranges from mild renal impairment to severe renal failure requiring dialysis or renal transplantation. The duration of the disease is over three months and renal function recovery is not expected. It is now renamed **Chronic Kidney Disease (CKD)** to stress the fact that the disease severity varies from mild to severe.[1]

In contrast, acute renal failure refers to the condition with sudden deterioration in renal function. With adequate treatment, good functional recovery is expected in many cases. Since there is a spectrum of severity, the condition is now renamed **Acute Kidney Injury (AKI)** as the word 'failure' would confer an impression of severe kidney impairment. It is stratified into three stages according to the KDIGO (Kidney Disease: Improving Global Outcomes) guideline.

AKI is a significant global problem with a disease prevalence of 1% to 25%, depending on the standard of definition of AKI.[2] It accounts for 3.2% to 9.6% of hospital admissions, with overall in-hospital mortality rate of around 20% and up to 50% in intensive care unit patients.[3] The development of AKI adversely affects the outcome even in cases with only a small decrease in glomerular filtration rate. Despite advances in intensive care and dialysis techniques in past decades, there was no significant improvement in the prognosis of AKI.[2] **Global awareness for AKI is needed, therefore the International Society of Nephrology and the International Federation of Kidney Foundation organized the 8th World Kidney Day on March 14, 2013 with the theme on AKI.**

Diagnosis of AKI

The clinical presentation of AKI includes the decrease in urine output and renal function as measured by the serum creatinine. The course is divided into the stage of onset, oliguric phase, diuretic phase and the stage of recovery. During the oliguric phase, there may be clinical signs such as puffiness of face, ankle oedema or pulmonary oedema.

AKI is now defined as increase in serum creatinine by 50% within 7 days, increase in serum creatinine by 26.5umol/L within 2 days or oliguria. Staging is based on the serum creatinine or urine output.(Table 1) Serum creatinine is used instead of using the eGFR by the MDRD equation as in CKD because the serum creatinine is changing over days and the equation only works for patients with stable creatinine concentration.

AKI Stage	Serum Creatinine	Urine Output
Stage 1	serum creatinine ≥ 1.5 to 1.9 times baseline OR ≥ 26.5umol/L increase	< 0.5ml/kg/hr for 6-12 hours
Stage 2	serum creatinine ≥ 2.0 to 2.9 times baseline	< 0.5ml/kg/hr for ≥ 12 hours
Stage 3	serum creatinine ≥ 3 times baseline OR ≥ 353.6umol/L OR treatment with renal replacement therapy	< 0.3ml/kg/hr for ≥ 12 hours OR oliguria for ≥ 12 hours

Table 1: Staging in Acute Kidney Injury

AKI Biomarkers

Currently serum creatinine and the urine output rate are the basis for the diagnosis of AKI. Unfortunately, serum creatinine starts to rise only when over 50% of the renal function is lost. Hence creatinine increase occurs late in the course of the disease and the clinician may not be alerted. Attempts had been made to identify urine or blood biomarkers which can help the early diagnosis of AKI. They detect cellular damage and may enable AKI to be detected up to 48 hours earlier then by the rise of serum creatinine. Such molecules include kidney injury molecule 1, neutrophil gelatinase associated lipocalin (NGAL) and

Figure 1 – 3. Performing the NGAL test in clinic

interleukin-18. NGAL is a promising candidate. It is a 25 kDa microalbumin-related protein and is present in the renal tubules in low concentration. During AKI, the expression is greatly up-regulated and its concentrations in the blood and urine were greatly elevated within a few hours, thus constituting early warning of AKI. The NGAL test can be done in the clinic with an automated machine about the size of a small ECG machine. The user puts a drop of whole blood into a test pad and then inserts the pad into the machine. The result would be available in a few minutes and can be performed by a trained nurse. (Fig. 1 to 3)

Causes of Acute Kidney Injury

The causes of AKI are classified into pre-renal, renal and post-renal causes. It would be more useful to the practicing doctors if the causes are grouped according to clinical settings, i.e. whether the patient is seen in the clinic ('community') or the hospital as the scenarios are quite different.

AKI in the community

AKI patients attending a doctor's clinic usually suffer from a mild form of AKI. They usually present as fluid retention like puffiness of face and ankle oedema. The most common cause is drug induced AKI and the most common culprits are non-steroidal anti-inflammatory drugs (NSAIDs) and some Chinese herbal medicine.

NSAIDs

NSAIDs are commonly used in clinics. They are used for the treatment of joint pain, muscle ache, ureteric colic, headache or fever. Examples of the group include ibuprofen, ketoprofen, diclofenac sodium and naproxen. Apart from the gastrointestinal side-effects, they are usually well tolerated. Selective cyclooxygenase-2 (COX-2) inhibitors have much less gastric side effects. **It should be noted that COX-2 inhibitors do have nephrotoxicity potential**. Since they can be used in high doses due to good gastric tolerance, the patient may suffer from severe nephrotoxicity.

To prevent AKI, NSAIDs should be prescribed with caution. When high potency NSAIDs are used, it is a sound advice that it should start with a low dose and the duration should be kept to the minimum. The following patients are at risks of developing AKI with NSAIDs and they should be monitored carefully:

- Elderly patients
- Patients with pre-existing renal impairment
- Patients with hypertension, heart failure and diabetes mellitus

One special consideration is gouty arthritis. Attacks are intermittent but each attack is very painful. During an attack, potent NSAIDs are frequently used. One such preparation is etoricoxib which can bring about pain relief quickly and effectively. Because of its potency, the renal function should be monitored as some patients develop anuria with the medication.

Allopurinol will prevent or reduce the frequency of attacks. It is not nephrotoxic but it needs to be taken continuously. For those patients with infrequent attacks (e.g. once per year), they might prefer life style modifications only (usually not successful) and receive NSAIDs treatment when needed. However, for those with frequent attacks, each treatment may bring about some degree of renal damage and the cumulative effect may be significant. For these reasons, the author recommended the following patients to take allopurinol continuously:

- Those patients at risk of AKI
- Those patients with frequent attacks
- Those patients with tophi (Fig. 4)
- Those patients with renal stones, especially those with stones' visual on the ultrasound but not seen in plain X-ray

Some patients might develop gouty attack when started on allopurinol due to a sudden drop in uric acid level. For this reason, it would be advisable to 'cover' the patient with colchicine for a period of three months. (Colchicine is not an analgesic and is only effective in gout.)

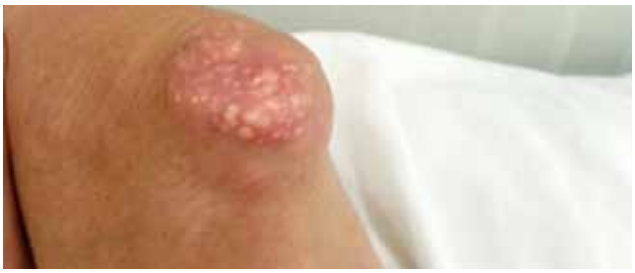

Figure 4. Tophi in a patient with gouty nephropathy. The uric acid can be clearly seen.

Chinese herbal medicine

Chinese herbal medicine is usually considered safe by the public but some herbs contain aristolochic acid (馬兜鈴酸), which is nephrotoxic. The author recently saw a patient with sudden renal deterioration and hyperkalemia and the only plausible cause was the herbal medicine which he recently took for constipation. The prescription was reviewed (Fig. 5) and it contained an item 木通 which can be 川木通 or 關木通 . 川木通 is the stem of *Clematis* species and is non-toxic, but 關木通 is the stem of *Aristolochiae manshuriensis* and contains aristolochic acid. It was possible that the patient was dispensed with the wrong preparation. The patient made good recovery upon stopping the medicine.

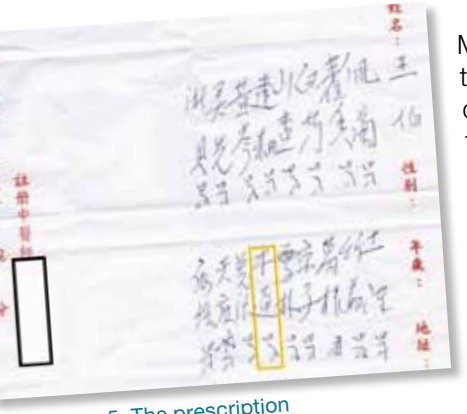

Figure 5. The prescription

Obstruction

Mechanical obstruction to the urinary flow usually develops gradually and the commonest cause in a clinic setting is the benign prostate hyperplasia (BPH). The patient usually has history of lower urinary tract symptoms like nocturnal frequency and urgency, and later presents as acute retention of urine. The diagnosis was made by feeling the enlarged bladder. Abdominal ultrasound would be useful to study the prostate and look for the presence of hydronephrosis. Catheterization in the clinic immediately relieves pain and obstruction. (Fig. 6)

Figure 6. (a) A grossly distended bladder in BPH (b) Catheterization in the clinic

AKI in hospitals

AKI in hospitals is usually a multifactorial entity.

Pre-renal AKI is caused by reduced renal perfusion, and common causes include gastrointestinal bleeding and diarrhea. Intra-operative fluid loss, if not adequately corrected, would also lead to AKI. Tests like the fractional excretion of sodium may help in the diagnosis. However, the diagnosis can be made from the history and by reviewing the hospital charts. Fluid status can be assessed clinically at the bedside. If the patient is found to be volume depleted, a saline challenge test can be done. 500ml of normal saline was infused with monitoring of the urine output and the cardiovascular status. If the urine output is restored, the condition is pre-renal AKI. Hence it is sometimes said that pre-renal AKI is a *retrospective* diagnosis. If oliguria persists, renal tubular necrosis has developed and the infusion should be stopped to prevent fluid overload. It might be useful to insert a central line through internal jugular vein to monitor the central venous pressure. If facilities are available, ultrasound guide during the procedure is advised to prevent complications because the patient is sick and vulnerable already.(Fig. 7)

Figure 7. Ultrasound guide in bedside CVP insertion

AKI caused by drugs

Drug-induced AKI occurs in about 20% of the hospital cases. Apart from NSAIDs, iodine containing X-ray contrast is another common offender. There are various medications claiming to prevent contrast induced nephropathy, including N-acetylcysteine and sodium bicarbonate. The best policy is the avoidance of dehydration and look out for risk factors like elderly age, diabetes mellitus, hypertension and pre-existing

renal impairment. A normal saline solution of 1mL/kg/h administered 12 hours before the procedure and then 12 hours after the procedure is recommended for most patients.

The commonest cause of renal cause of AKI is septicemia which was caused by sepsis and hospital acquired infections. AKI is usually part of the picture of the multi-organ failure and the mortality rate is high. Rarer causes include rapidly progressive glomerulonephritis, vasculitis and interstitial nephritis. Urine microscopy may reveal active urine sediments like red cells, white cells and casts. Serological tests such as the ANCA (anti-neutrophil cytoplasm antibodies) are useful. **For AKI patients with causes not readily found, a renal biopsy would be most useful for the diagnosis.**

In developing countries, infections such as malaria, leptospirosis, dengue hemorrhagic fever and hanta virus infection causing AKI are common. These are rare in Hong Kong. Dengue fever had been reported during the development of Ma Wan Island. Lam and Kan reported two cases of leptospirosis in two triathlon runners in 2004 [4]. The author reported 2 cases of AKI complicating malaria infection in his review of acute haemodialysis in a renal unit. Both patients required haemodialysis support and they recovered.[5] **Since malaria can be contacted outside Hong Kong, any patient who develops fever and AKI with history of travelling to malaria area should be investigated for malaria**.

Post-renal causes

Prostate obstruction and malignancies with secondaries affecting both ureters may present as acute-on-chronic obstruction. A patient with a single functioning kidney may have the kidney obstructed by a ureteric stone.

Treatment of AKI

The mainstay of the management of AKI is to treat the primary causes: stop the offending medications, restore the blood pressure and renal perfusion, treat the sepsis and remove the obstruction. Supportive treatment includes monitoring the urine output, blood pressure and renal function. Dietary protein and potassium restriction will be needed to control the blood urea and potassium. Water restriction may be needed during the oliguric phase to prevent fluid overload. Dialysis will be indicated under the following circumstances:

- Urea > 30mmol/L and creatinine > 700umol/L
- Refractory hyperkalaemia or rising potassium level
- Pulmonary oedema
- Severe metabolic acidosis producing circulatory compromise

The decision for institution of dialysis is a clinical one. If the patient showed clinical signs of deterioration or uremic symptoms such as encephalopathy or pericarditis, dialysis should be started without delay.

Temporary dialysis support is lifesaving as it tides the patient over until the renal function returns. Peritoneal dialysis or haemodialysis had been used for this purpose, and in developing countries, peritoneal dialysis might be the only option available. Haemodialysis is preferred or indicated under the following circumstances:

- Peritoneal dialysis might not be feasible after a recent abdominal operation
- If the rate of serum urea raise is high, such as in sepsis or in burn patients ('hypercatabolic state'), haemodialysis is preferred as the rate of toxin removal is much higher
- Haemodialysis is more comfortable to the patient and this is an important consideration if the patient is suffering discomfort from the underlying causes already

The SLED
(Slow, Low Efficiency Dialysis)

In those patients with multi-organ failure, the blood pressure may be unstable or low. Putting the patient on conventional haemodialysis may cause further cardiovascular disability and was usually considered dangerous. In the past decades, haemofiltration had been proposed as an alternative renal replacement therapy. The principle is to take the blood out of the

patient to a 'haemofilter' where some of the plasma water is filter out and replaced with replacement fluid. The process has to be done continuously in days and is therefore called Continuous Renal Replacement Therapy (CRRT). While this procedure may provide greater cardiovascular stability, special machines and specially trained personnel are needed. The patient needs to stay in the intensive care unit and the cost is very high. Since anticoagulation is needed throughout the process, there is additional risk of bleeding.

In recent years, the technique of SLED as the dialysis support for AKI was receiving increasing attention. Since the patients' cardiovascular status was fragile, removal of fluid and toxin level should be gradual. In a conventional dialysis, blood was taken out of a patient at a rate of some 250ml/minute and typically around 3 litres of fluids were removed in 5 hours (i.e., fluid removal rate at 0.6L/hour). In SLED, the efficiency of the dialysis was purposely reduced by changing to a less efficient dialyser, reducing the blood flow rate to some 150ml/minute and reducing the dialysate flow from 500ml/minute to 300ml/minute. Thus the patient would be exposed to less urea level fluctuation. The dialysis duration was extended to 6 hours and the amount of fluid removed was reduced to some 1.5 litres, i.e., at a rate of 0.25L/hour. Since the fluid removal rate is reduced, hypotension episodes are infrequent. (Fig. 8) However, the dialysis had to be daily instead of on alternate days. Since the dialysis is done daily, there is less fluid and toxin accumulation. The charge for an SLED is the same as conventional haemodialysis. For this reason, it is much cheaper than CRRT which has to be done in an ICU. The patient can be treated in a general ward and be transferred to the renal unit for dialysis daily. Studies had shown that the results of SLED and CRRT are the same.

Summary

AKI is receiving increasing attention recently for the following reason:

A significant percentage of patients in the hospital develop AKI globally with severe impact on the outcome. Timely correction will cause recovery of renal function but delayed correction may lead to permanent damage.

In a clinic setting, it presents as acute loss in renal

Figure 8. The SLED setup

function and the cause of the problem can only be elucidated by careful history taking. **In Hong Kong, NSAID is the commonest cause of AKI**. It can also occur in the hospital as a complication of heart failure, septicemia or fluid loss. AKI biomarkers are under investigations and the NGAL test appears to be promising.

It was used to believe that AKI patients will have full recovery of the renal function with treatment. However, it is now known that if the damage from AKI is severe or if the damage is repeated, the repair may not lead to complete recovery and some degree of fibrosis will result. The fibrosis will predispose the kidneys to progress to CKD and some of them may end up in ESRD. **Prevention and global awareness of AKI are therefore needed**.

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Q&A Self-assessment Questions

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Answer these on page 14 or make an online submission at: www.hkmacme.org

Please indicate whether the following statements are true or false.

1. Full recovery of renal function is guaranteed after treatment of AKI.
2. Calculating eGFR by MDRD equation is useful in the diagnosis of AKI.
3. Creatinine is not sensitive in detecting renal function lost in initial phase of AKI.
4. COX-2 inhibitors, unlike other NSAIDs, do not have concerns over its nephrotoxic effect.
5. Chinese herbal medicine is one of the special local causes in Hong Kong that should be bared in mind when sudden renal deterioration is seen.
6. When obstructive cause is diagnosed in an AKI patient, abdominal ultrasound would be useful in further studying the cause and complications of the obstruction.
7. The commonest cause of renal cause of AKI is glomerulonephritis.
8. Dietary protein and potassium restriction are needed in the management of AKI.
9. If the rate of serum urea raise is high, SLED is preferred over haemodialysis.
10. SLED can provide greater cardiovascular stability.

Answer to July 2013
Current Approach in the Diagnosis and Treatment of Peripheral Arterial Disease (Part 2)

1.F 2.T 3.F 4.T 5.F 6.T 7.T 8.T 9.F 10.T