CME

Approach to managing elevated creatinine

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ABSTRACT

OBJECTIVE To describe a systematic approach to finding the underlying cause of an elevated creatinine level.

QUALITY OF EVIDENCE This diagnostic approach is based on a synthesis of information from reference works on nephrology, articles found through a MEDLINE search, and the author's personal experience.

MAIN MESSAGE Elevated creatinine levels suggest the differential diagnosis of renal failure (RF). History and a complete physical examination are important, keeping in mind that RF is often asymptomatic in the early stages. After repeating the creatinine test to verify results, baseline tests should be ordered to identify the cause of the RF. Comparing results of serial tests is essential for determining whether RF is acute or chronic, stable or progressive. An ultrasound scan is particularly useful for eliminating an obstructive cause; the size of the kidney can indicate whether disease is acute or chronic. Complementary blood tests and imaging studies might be useful.

CONCLUSION Diagnosing and managing RF can appear complex, but a systematic approach will help you find the cause and treat the condition.

RÉSUMÉ

OBJECTIVE Cet article présente une approche clinique systématique à l'identification de la cause sous-jacente d'une valeur de créatinine élevée.

SOURCES D'INFORMATION La démarche diagnostique présentée est fondée sur une synthèse de référence en néphrologie, d'articles retrouvés à l'aide de MEDLINE, ainsi que sur l'expérience personnelle de l'auteur.

PRINCIPAL MESSAGE La découverte d'une créatinine élevée doit nous amener à réfléchir au diagnostic différentiel possible de l'insuffisance rénale (IR). Tout comme dans d'autres affections, il est important de faire un questionnaire et un examen complets en se rappelant que l'IR est souvent asymptomatique à un stade précoce. Après avoir répété la mesure d'une créatinine élevée pour vérifier les résultats, on prescrit un bilan de base pour identifier la cause de l'IR. La comparaison avec des valeurs antérieures de créatinine est primordiale pour déterminer si l'IR est aiguë ou chronique, stable ou progressive. Une échographie est particulièrement utile pour rapidement éliminer une cause obstructive. La taille des reins peut nous orienter vers une atteinte aiguë ou chronique. Les tests sanguins et d'imagerie complémentaires peuvent être utiles.

CONCLUSION L'IR peut paraître complexe, mais avec une approche systématique, on peut en trouver la cause et traiter cette dernière le cas échéant.

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Case

You have recently seen a 59-year-old woman with hypertension. She is also diabetic, and she smokes a packet of cigarettes a day. You receive results of her blood tests and note immediately that her creatinine level is 179 µmol/L, her potassium level is 4.8 mEq/L, and her hemoglobin is 125 g/L. Her glycosylated hemoglobin is 6.0%; her lipid levels are normal. What do you do about the abnormal creatinine results?

Renal failure (RF) has a range of clinical presentations. Some patients have symptoms directly related to the kidneys, such as hematuria or pain in the kidney area. Others have nonrenal symptoms, such as edema, hypertension, or signs of uremia. Most patients with compromised renal function, however, are asymptomatic and are discovered opportunistically during routine blood tests. This article presents a systematic approach to this problem with a focus on chronic renal failure (CRF).

An elevated creatinine level in itself will not tell us whether we are dealing with acute renal failure (ARF) or CRF. Acute renal failure will be discussed only briefly in this article (**Table 1**).

Quality of evidence

The diagnostic approach presented here is based on a synthesis of information from reference works on nephrology, articles found in various scientific publications listed on MEDLINE, and the personal experience of the author. Most of the laboratory tests recommended (**Tables 2** and **3**) are based on a consensus statement on RF published in 1999[1] and on a synthesis of the consensus reached in the Dialysis Outcome Quality Initiative,[2] a clinical practice guideline published by the National Kidney Foundation.

Causes of RF

The current clinical approach is to divide the causes of RF into three categories: prerenal, renal, and postrenal or obstructive.

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Table 1. Factors suggesting acute and chronic renal failure

ACUTE RENAL FAILURE
Sudden onset of fever or hematuria
Sudden aneurysm (suggests an obstruction)
Hypovolemia
Sepsis
Episode of hypertension
Recent potentially nephrotoxic agents taken
No anemia*
No hypocalcemia
No hyperphosphatemia
CHRONIC RENAL FAILURE
Previous confirmed nephropathy
Already diminished creatinine clearance rates
Atrophic kidneys (<10 cm on ultrasonography)
Normochromic, normocytic anemia
Hypocalcemia
Hyperphosphatemia

**Anemia is absent also in chronic renal failure patients with polycystic renal disease.*

Table 2. Stages of renal failure estimated by glomerular filtration rates: *Renal function must be stable for the calculation to be valid. Use lean weight estimated by body mass index (weight divided by height squared [kg/m^2]).*

STAGES OF CHRONIC RENAL FAILURE	GLOMERULAR FILTRATION RATES (ML/MIN)
Mild	60-90
Moderate	30-60
Severe	10-30
Terminal	<10

Cockroft-Gault formula for estimating creatinine clearance in mL/min based on serum creatinine

$$\text{Men:}\quad \frac{140 - \text{age (y)} \times \text{weight (kg)}}{\text{serum creatinine (µmol/L)} \times 0.8}$$

$$\text{Women:}\quad \frac{140 - \text{age (y)} \times \text{weight (kg)} \times 0.85}{\text{serum creatinine (µmol/L)} \times 0.8}$$

Prerenal causes. Prerenal problems derive from a decrease in glomerular perfusion. They are caused by a depletion in blood volume or relative hypotension. The hypoperfusion could be secondary to blood loss or to excessive skin damage (such as with a deep burn) or decreased perfusion due to congestive heart failure, cirrhosis, or hypovolemic shock.

Table 3. Baseline tests to order when an elevated creatinine level is found

STAGE 1
Look in the chart for previous creatinine clearance rates
Redo the creatinine test
STAGE 2
Baseline laboratory tests
• Creatinine clearance (calculated with the Cockcroft-Gault formula or by 24-hour collection*)
• Urinalysis
• Urinary sediment
• Measurement of diuresis over 24 hours (if anuria)
• 24-hour urine collection to test for clearance of creatinine and proteins
• Urea
• Electrolytes
• Complete blood count
• Glycemia
• Bicarbonate
• Calcium and phosphorus
• Protein and albumin
• Electrophoresis of proteins
BASELINE IMAGING STUDIES
• Renal ultrasonography

**The 24-hour collection is more precise but more complicated. It allows you to calculate proteinuria and creatinuria.*

Renal causes. This category is subdivided into vascular diseases, glomerular diseases, and tubulo-interstitial diseases.

Vascular diseases: Vascular problems can be separated into two subclasses, those caused by ARF and those caused by CRF. Principal acute causes are vasculitis, malignant hypertension, scleroderma, and thromboembolic diseases. Among chronic vascular causes are benign nephroangiosclerosis and stenosis of the renal arteries (leading to ischemic nephropathy).

Glomerular diseases: These diseases present clinically two ways, as a nephrotic syndrome or as a nephritic syndrome. The first manifests itself clinically through severe proteinuria (usually >3 g/d). The second manifests itself through a variable degree of proteinuria, hypertension, and active urinary sediment (hematuria, leukocyturia, and cellular cylinders).

Tubulo-interstitial diseases: These can also be acute or chronic. Frequent causes of ARF are acute tubular necrosis, acute interstitial nephritis, and a myelomatous kidney. Polycystic renal disease, vesicoureteral reflux, certain autoimmune diseases, and abuse of analgesics (including acetaminophen, acetylsalicylic acid, and nonsteroidal anti-inflammatory drugs) lead to chronic tubulo-interstitial conditions.[3]

Postrenal causes. An obstruction can occur at any point between the kidney and the end of the ureter. To cause RF in patients with kidneys that function relatively well initially, an obstruction must be bilateral if it is above the bladder.

Is it ARF or CRF?

After history and physical examination, what should we do next? The first thing is obtain previous creatinine results if they are available. They are very useful for determining whether our patient has ARF or CRF. For example, if we find that our patient, who currently has a creatinine level of 179 µmol/L, had a level of 155 µmol/L 2 years ago, she probably has slowly progressive CRF.

If no previous results are available, we must redo the tests to ensure that results are correct and to ascertain whether they are stable or increasing. After that, frequency of measurement will depend to a great extent on clinical context, on the degree of suspicion about each of the possible diseases, and on physicians' experience with renal diseases. Frequency of creatinine measurements was discussed by the group who originated the Canadian recommendations in 1999, and no consensus was reached.[1]

In our office, we do annual or biannual creatinine measurements in patients with mild, stable CRF and monthly measurements in patients with severe CRF (**Table 2**). In patients with rapidly increasing creatinine, testing might be necessary daily or weekly. If creatinine is rising rapidly, consultation with a nephrologist is needed.[4,5] The Canadian Nephrology Society recommends referring patients to a nephrologist if creatinine levels are >150 µmol/L (level III evidence).

Blood and urine tests

It is important to quantify the degree of RF, usually by evaluating the rate of glomerular filtration (**Table 2**). Creatinine levels themselves can be misleading, particularly when patients have little muscle mass or are extremely elderly. It is recommended that we use creatinine clearance as a way to evaluate degree of RF (level I evidence). It can be calculated using the Cockroft-Gault formula (**Table 2**) or using 24-hour collection (more precise but more cumbersome).

Baseline tests to order when an elevated creatinine level is found are shown in **Table 3**. Urinalysis is of prime importance because it can show, for example, whether there is hematuria, pyuria, or proteinuria, which we could then quantify with the aid of a 24-hour collection. Quantification of diuresis is equally useful, particularly when it is found along with anuria, which could be caused by a bilateral obstruction, a bilateral thrombosis of the renal arteries, or circulatory shock. Maintaining normal diuresis is in itself little use for making a diagnosis because diuresis often persists until a very advanced stage of CRF.

For baseline blood tests, a complete blood count is useful. Thrombopenia suggests thrombotic thrombocytopenic purpura (hemolytic uremic syndrome), leukocytosis suggests acute bilateral pyelonephritis, and eosinophilia suggests allergic interstitial nephritis or RF caused by an atheroembolism. Glycemia tests allow us to see evidence of unrecognized diabetes. Phosphocalcic tests will discover hypercalcemia, which can cause RF, or will suggest the presence of multiple myeloma. Electrophoresis of proteins should be part of the investigation for CRF to seek out multiple myeloma, particularly among patients older than 40 (level III evidence).

If baseline tests do not produce the information we seek, complementary tests are indicated (**Table 4**). These tests will be dictated by the clinical situation and the underlying pathophysiology of the various diagnostic possibilities that remain. Liver tests allow us to look for hepatitis with secondary glomerulonephritis or cirrhosis with RF secondary to a decrease in the volume of circulating blood. Although not directly associated with ARF, a creatinine kinase test allows us to eliminate severe rhabdomyolysis, which sometimes occurs in people who jump into tough sporting activities without training.

Table 4. Other investigations for renal failure: *Tests should be ordered according to the clinical situation.*

BLOOD TESTS
Immunity studies: antinuclear antibody, anti-DNA, rheumatoid factor, antineutrophil cytoplasm antibody, and C3 and C4 counts
Inflammatory studies: sedimentation rate, protein C–reactive
Serologic and infectious studies: hepatitis B surface antigen, HIV, hemocultures for Bence Jones' urinary protein, purified protein derivative
Test for eosinophiluria
Creatinine kinase
Liver tests: aspartate aminotransferase, alanine aminotransferase, bilirubin, and alkaline phosphatase
IMAGING STUDIES
Plain x-ray film of the abdomen
Intravenous pyelography*
Computed tomography scan*
Magnetic resonance imaging
Renal angiography*
Renal scintigraphy

**Risks are associated with contrast agents.*

Imaging studies

All the recommendations that follow are based on expert opinion or consensus (level III evidence), except when the text states otherwise.

Renal ultrasonography, one of the baseline tests, is the most useful examination for evaluating RF, particularly for eliminating an obstruction that can be easily removed. Ultrasonographic evidence of atrophic kidneys indicates CRF, even though normal-looking kidneys are found in patients with ARF and CRF (diabetes or multiple myeloma). You could also discover previously unsuspected polycystic renal disease. Adding a Doppler signal during ultrasonography allows evaluation of blood flow and might suggest thrombosis of the renal artery or vein.

A simple x-ray film of the abdomen allows us to search for radiopaque stones (that contain calcium, struvite, or cystine). Uric acid stones cannot be

seen because they do not contain calcium.

Endovenous pyelography is used less and less. It has been replaced by ultrasonography, which can usually give the same information without the dangers inherent in using contrast agents. Endovenous pyelography remains the test of choice, however, for seeking out renal papillary necrosis or a sponge kidney.

Spiral computed tomography has become the best investigation for detecting nephrolithiases[6] (level II evidence), but standard computed axial tomography is very sensitive for this purpose too. It is also useful for detecting thrombosis of the renal veins and for diagnosing polycystic renal disease.

Magnetic resonance imaging (MRI) can be used to look for stenosis of the renal arteries. It is much less risky than arteriography (because of the various contrast agents used and because there is no risk of atheroembolism). If you find a severe stenosis, certain criteria (eg, size of the kidney, condition of the vascular distal bed, and risks of the procedure) will help you decide whether it would be advantageous to proceed to an angioplasty.

Renal arteriography is useful if there is renal artery thrombosis or if you suspect narrowing of the arteries. It has the added advantage of being diagnostic and of indicating curative intervention with angioplasty for certain patients with renal artery stenosis.

Renal scintigraphy with or without captopril is often used as a screening test for renal artery stenosis, for example, when you suspect renovascular hypertension. Diethylenetriamine pentaacetic acid (DTPA) scintigraphy with furosemide can be used in certain cases to verify whether hydronephrosis is clinically significant.

Retrograde pyelography is rarely used these days for finding obstructions. It could be useful (because it avoids the toxicity of intravenous stain) for finding an obstruction in the sheath of the ureters when you do not see hydronephrosis on ultrasonography or in a patient with severe CRF in whom you suspect an obstruction.

Nephrologists will order renal biopsy in certain cases to identify the nature of an underlying infection, particularly when noninvasive tests have not had conclusive results (**Table 5**). Objectives of a biopsy are to establish a diagnosis, to help choose a treatment, and to determine the extent of acute (perhaps reversible) or chronic changes.

EDITOR'S KEY POINTS

- A systematic approach can help diagnose and treat the cause of an elevated creatinine level.
- Renal failure should be considered in the differential diagnosis.
- Serial test results will show whether renal failure is acute or chronic, stable or progressive. Treatment is based on findings.

POINTS DE REPÈRE DU RÉDACTEUR

- Une approche clinique systématique peut aider à l'identification de la cause d'une valeur de créatinine élevée.
- La découverte d'une créatinine élevée doit nous amener à réfléchir au diagnostic différentiel possible de l'insuffisance rénale (IR).
- La comparaison avec des valeurs antérieures de créatinine est primordiale pour déterminer si l'IR est aiguë ou chronique, stable ou progressive.

Table 5. Indications for renal biopsy: *Physicians should take into account clinical presentation and their degree of suspicion about the various diseases under consideration.*

Nephrotic proteinuria, except if attributed to diabetes
Certain cases of non-nephrotic proteinuria
Lupus nephritis (for diagnosis and for determining stage)
Certain cases of vasculitis
Unexplained acute renal failure
Isolated hematuria (rarely)

Back to the case

You order another creatinine test to check previous values. The control test result is 176 µmol/L; the chart shows a value of 140 µmol/L 4 years ago and 150 µmol/L 3 years ago. This suggests slowly progressive CRF. Other test results are normal except for a trace of protein in the urine and the discovery on ultrasonography of slightly atrophic kidneys (9.8 cm) and a thinning of the cortical layer. The clinical picture is compatible with nephroangiosclerosis in a patient who smokes and who has been hypertensive for a long time. We do not believe that diabetic nephropathy is the cause here because proteinuria would be seen before RF and because the kidneys are usually preserved in diabetic nephropathy.

Conclusion

Although RF can appear complex to diagnose and manage, a systematic approach will help you find the cause and treat the condition. The first step when you discover an elevated creatinine level is to confirm that it is not an error. Then you need to determine whether the level is stable, in which case you are probably dealing with CRF, or suddenly higher (ARF). In looking for the cause of RF, you need to keep in mind the classic division of causes into prerenal, renal, and postrenal, and the subdivisions of each.

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For further reading

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