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A review of important tips on chronic kidney disease for 21st century general practitioners

Akinwumi Ayodeji Akinbodewa *

Renal unit, University of Medical Sciences Teaching Hopsital, Ondo City, Ondo State, Nigeria.

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Abstract

One of the major goals of the International Society of Nephrology is prevention of chronic kidney disease. It is a slow-burning, unrelenting disorder that is largely asymptomatic in the very early stages thus leaving room for silent progression to end stage if left unchecked. Sub-optimal knowledge of the disease, non-screening for renal markers and late referral are among physician-related factors that hinder patients from accessing early intervention by nephrologists. Here, we draw attention of General Practitioners to current principles in early identification of chronic kidney disease. It is a multi-systemic disease capable of mimicking other organ-system disorders hence requires a high index of suspicion. The updated Kidney Disease Outcome Quality Initiative definition, diagnosis and staging of chronic kidney disease has improved early detection, prevention and retardation of the disease among population at risk. Routine renal function and structure evaluation should be conducted for all new patients presenting for care, be it out-patient or admission. Serum creatinine and albuminuria are the two most important markers required for early diagnosis and staging of CKD; unlike previously thought, urea does not rank high among markers of chronic kidney disease. History of nocturia, can be an important early pointer to chronic kidney disease, especially among population at risk. Presence of normal blood pressure, normal urine volume, absence of body swelling and sonographically normal renal sizes do not exclude chronic kidney disease where serum creatinine is elevated. Improved knowledge of chronic kidney disease among non-nephrology physicians can significantly reduce the global burden of the disease.

Keywords: Chronic kidney disease; Early detection; Prevention; Tips; General practitioners

1. Introduction

Chronic Kidney Disease (CKD) is a slow-burning, unrelenting disease that is associated with significant morbidity and mortality, and a high degree of financial burden on sufferers, care givers and the community [1]. In more than 90% of cases, CKD is asymptomatic in the very early stages thus leaving room for quiet progression to the latter irreversible stages if left unchecked. Early detection should normally provide the Nephrologist with sufficient room to introduce interventional strategies that delay progression of the disease to End Stage Renal Disease (ESRD). [2] As a matter of fact, the 2012 KDIGO guideline on evaluation and management of CKD stated on page 19, "chronicity is not synonymous with irreversibility. In some cases, CKD is entirely reversible, either spontaneously or with treatment, and in other cases, treatment can cause partial regression of kidney damage and improvement in function" [2].

However, most patients are not benefiting from these interventions because they are often referred late to the Nephrologist, that is, if at all [3-4]. One study showed that 50% of cases of late presentation was due to physician-related factors in which case either the patients at risk were not screened for renal dysfunction or there was non-referral to Nephrologists in the early stages of the disease [5]. Another study demonstrated significantly lower knowledge of CKD among General Practitioners (GPs) when compared to Specialists thus corroborating physician-related factors as

* Corresponding author: Akinwumi Ayodeji Akinbodewa

important determinants of late referral [6]. Indeed the study by Adejumo et al. indicated that nearly 50% of the CKD patients in one centre in Southwest Nigeria were referred from GPs in private hospitals and secondary health facilities. [7] This burden of evidence shows why GPs need regular update on CKD as they occupy an important place in early detection and prevention of CKD.

The International Society of Nephrology (ISN), the umbrella body for the global nephrology community did identify deficiencies in physicians' awareness of CKD as a barrier to reducing the burden of CKD globally thus choosing the theme, "Kidney Health for All" during her World Kidney Day programme in 2022 with one of its aims thus stated: "to encourage and support primary care physicians to improve their recognition and management of patients with CKD across its entire spectrum from prevention and early detection to its secondary and tertiary prevention and kidney failure care" [8]**.** Up until now, however, the spate of late referral of CKD patients to Nephrologists remains very high in Nigeria and elsewhere with many presenting when they have either developed acute, life-threatening complications or require dialysis at ESRD [6-7, 9]**.** This places a huge burden on Nephrology and dialysis teams globally and contributes significantly to financial, social and psychological burdens on patients and their significant others.

In light of the mission of the ISN, in which authors have previously provided primary care physicians with tips on acute kidney injury in a previous publication as part of efforts on continuing medical education for medical doctors [10], the following tips are thus highlighted as part of continuing efforts to further equip GPs (who generally have the first contact most patients) with knowledge on another form of kidney disorder that portends poor outcome for individuals if detected late.

An internet-based search of MEDLINE, Medscape, Web of Science, Science Direct, Scopus, Research gate and Google Scholar databases was conducted using the following keywords, "primary care physicians", "General Practitioners", "tips on chronic kidney disease", "kidney disease prevention", "early detection of chronic kidney disease", "knowledge of chronic kidney disease". Studies that was restricted to Specialist nephrologists or included knowledge of CKD among non-physicians (nurses, other healthcare workers) were excluded. Studies that was restricted to, or included knowledge of acute kidney injury or kidney transplantation were excluded. Studies that compared knowledge between GPs and Specialist nephrologists were included where relevant.

In order to reach the GPs who are the primary target of this review, the use of technical terminologies in renal medicine was restricted as much as possible, being replaced by a direct and practical approach with utilization of easy-to-digest guiding tips and lesson summary (otherwise known as take home points) at the end of each section.

2. Tip number 1: change in definitions and concepts

As a matter of priority, GPs should take note of important changes in nomenclature. Primarily, the term, chronic renal failure (CRF) has long been replaced with the new terminology, chronic kidney disease (CKD) which is broader and more encompassing in scope. The term, CRF used to give an impression of irredeemable kidney damage thus condemning the patient to ESRD with only renal replacement therapy as a viable option. This earlier conclusion was probably based on the fact that many patients presented late to the hospital which corresponded roughly to the stage where the kidney damage had reached a state of irreversibility.

Table 1 GFR* categories in chronic kidney disease [11]

Category	GFR (ml/min/1.73m^2)	Interpretation
Stage 1	≥90	Normal or high
Stage 2	60-89	Mildly decreased
Stage 3a	45-59	Mildly to moderately decreased
Stage 3b	30-44	Moderately to severely decreased
Stage 4	15-29	Severely decreased
Stage 5	<15	Kidney failure

*Glomerular filtration rate

In contrast, the new terminology, CKD points attention to early detection and prevention of CKD rather than treatment considering the staging of severity of damage from mild through ESRD (table 1) [11]. Staging of the disease naturally

heightens proficiency in early detection of CKD among people at risk such as those with hypertension, diabetes, obesity, family history of CKD, low birth weight, obesity, significant smoking and alcohol consumption, use of recreational drugs, prior AKI, obstructive sleep apnoea etc. [12] . We consider this an important first step because studies have shown low level of knowledge of the relatively new NKF-KDOQI definition of CKD among GPs which ranges between 38.8% and 58.8% depending on the part of the world where the studies were conducted [6, 13-14]. In effect, CKD is defined as (i) abnormalities of kidney structure or function, present for > 3 months, with implications for health [11]. *It is characterised by structural or functional abnormalities of the kidney - with or without decreased glomerular filtration rate (GFR)* [11]. Broken down into simple English, it means that CKD diagnosis can be made based on structural damage arising from any or a mixture of multiple cysts, stone or tumour in the kidney or congenital renal anomaly alone and not just on persistent elevation in serum creatinine (and consequently, reduced eGFR). These may manifest as persistent significant proteinuria (UPCR >0.3) or persistent haematuria.

The new NKF-KDOQI definition and staging therefore alert the GP to the fact that patients with CKD can be asymptomatic for months to years before they progress silently to ESRD (stage 5, eGFR < 15ml/min/1.73m^2) and so above kidney anomalies must be searched for in people at risk [4].

Lesson: New definition for CKD, its pathogenesis and staging now help prevention, early detection and retardation of CKD progression.

3. Tip number 2: prioritize screening for CKD

Every patient should undergo renal function evaluation at first contact with the GP, especially population at risk of CKD [11]. The key phrases of emphasis here include, “at first contact”, and “population at risk”. “At first contact” because onset and progression of CKD is a function of time and therefore early detection through prompt screening is important in arresting these. Secondly, collection of such data at first arrival to clinics will serve to create a robust national data pool on baseline renal function for reference and research. “Population at risk” because the potential for development of CKD has been associated with certain genotypes and phenotypes. As CKD is clinically silent and asymptomatic the latter stages, all people at risk should be routinely screened for CKD as early as possible [12, 15]. The NKF-KDOQI guideline employs serum creatinine and albuminuria as reliable surrogate markers to diagnose and stage the severity of CKD (tables 1 and 2). In order to achieve this, the serum creatinine sample should be taken in the stable state which in our experience corresponds approximately to when the patient is able to produce a minimum of 1,000ml of urine per day with absence of on-going features acute decompensation of kidney function. The individual’s eGFR can then be obtained by means of the chronic kidney disease-epidemiology (CKD-EPI) equation [16]. The calculator can be downloaded as an App on every smart phone.

Table 2 Albumin categories in chronic kidney disease [11]

Category	ACR* (mg/g)	Interpretation
A1	<30	Normal to mildly increased
A2	30-300	Moderately increased
A3	>300	Severely increased

*Albumin-to-creatinine ratio

Another important consideration of note is the assumed role of serum urea in determining severity and intervention in CKD. Most non-nephrology physicians often confuse the term, “uraemia” with the word, “urea”. While serum urea rises as uraemia worsens, it is not as reliable as creatinine in determining renal function status, prognostication and monitoring of progress during treatment as serum urea level varies with both internal and extraneous factors such as level of hydration, exercise, high protein diet, drugs and infections unlike serum creatinine [17].

Lesson: serum creatinine and albuminuria are the two main tests required in the diagnosis and staging of CKD; urea is not as reliable as previously thought.

4. Tip number 3: clinical markers of early detection

Medical doctors, by virtue of training, are familiar with the more dramatic and obvious symptoms of CKD such as body swelling, oliguria, vomiting, diarrhoea, altered sensorium, easy fatigability and dyspnoea. However, these manifest

when patients experience acute decompensation of kidney function or have reached ESRD without adequate dialysis. As early detection of CKD and retardation of its progression to ESRD is the desired objective of ISN, GPs need to be well aware of some of the earliest clinical features of CKD such as nocturia and proteinuria.

Nocturia is arguably the single most important symptom associated to CKD in the early stages as besides it, there is hardly any other symptom that points to CKD during history taking [17]. GPs must therefore have a high index of suspicion and search for this very key symptom by taking a concise and detailed history.

Nocturia is defined as frequency of urine void that is ≥ 2 times during the night [18]. The mechanism that leads to nocturia is thought to be a CKD-induced deficit in urinary concentration and increased salt excretion [19]. It is important to exclude urine voided just before bedtime and morning time while eliciting the number of times patient wakes up to urinate.

All people at risk of CKD should be asked routinely about nocturia. However, the GP must take care to rule out other causes of nocturia such as polydipsia and starchy food at night, ageing, pregnancy, use of drugs (diuretics, cardiac glycosides, demeclocycline, lithium, calcium channel blockers, NSAIDs, methoxyflurane, phenytoin, propoxyphene and excessive vitamin D), diabetes, enlarged prostate, obstructive sleep apnoea, urinary tract infection, severe heart failure and bladder disorder such as interstitial cystitis, bladder malignancy and bladder over-activity [19]. The presence of any of these does not rule out CKD as co-morbidity has been known to occur.

Lesson: In the absence of other causes, persistent nocturia in people at risk is highly indicative of early CKD until proven otherwise.

5. Tip number 4: clinical mimicry and red flags

CKD, being a multi-systemic disease, is capable of masquerading like many other diseases depending on the organ system involved at the time of acute decompensation. Therefore GPs need to be on the look-out for confounding symptoms and signs especially when the so-called symptoms or "disease" is not abating with conventional treatment as expected.

5.1. Haematological mimicry

One of the most common presentations of CKD is anaemia (haemoglobin concentration <12g/dl in women and <13g/dl in men) which can manifest as easy fatigability, dyspnoea, headaches and depression [20]**.** The most notable cause of anaemia in CKD is deficiency of endogenous erythropoietin following significant run-off of peritubular renal tissue that is responsible for its synthesis [21]**.** Uraemic toxins are also known to interfere with formation of red blood cells and shorten life span of red cells due to heightened red cell fragility. They also lead to thrombocytopathy and thrombocytopaenia which promote internal haemorrhage and progressive glomerular damage [22]. CKD patients can therefore present to the GP for the first time with gum or mucosal bleeding, haemothorax or even haemopericardium.

Even though it is rare for platelet dysfunction to manifest clinically in CKD patients due to greater production of thrombopoietin (platelet modulating hormone) by the liver, evaluation of patients for thrombocytopathy is important as it may be the first pointer to renal diseases such as lupus nephritis (SLE), thrombotic thrombocytopaenic purpura (TTP) or haemolytic uraemic syndrome (HUS) [23-24]. Arogundade et al reported two cases of patients with SLE and TTP with low platelets who required urgent therapeutic plasma exchange [25]. There are instances where patients would have received multiple blood transfusion before a renal function test is requested. For instance, in one study, 29.3% of CKD patients had been transfused with blood before referral to the Nephrologist [9]. Adults presenting to the clinic with anaemia in the absence of active blood loss or fever should as a matter of first principle be screened for CKD among other haematological disorders.

5.2. Gynaecological mimicry

Men and women who have difficulty in achieving pregnancy should be screened for CKD as part of investigation panel for infertility. Women in this category are likely to have menstrual anomalies ranging from hypomenorrhoea to amenorrhoea while the men may have reduced libido and poor semen quality. The association between CKD and infertility among men and women has been attributed to a number of factors which include accumulation of uraemic toxins, impairment of ovarian function, reduced ovarian reserve, hyperprolactinaemia, hypergonadotropic hypogonadism, impaired spermatogenesis, direct testicular damage, reduced libido and depression among others [26-27].

An important pointer to possible CKD in the obstetric setting is presence of severe, seemingly recalcitrant high blood pressure in pregnancy (aka renovascular hypertension) as this could signify previously undiagnosed glomerular

disease, renal artery stenosis or atherosclerotic renovascular disorder as a cause of secondary hypertension in pregnancy [28]. Apart from the difficult to control blood pressure, they present with any, or a combination of the following: headaches, altered sensorium, seizures, haematuria, proteinuria and body swelling which is indicative of accelerated (aka malignant) hypertension. This is important because the presence of renovascular hypertension impacts significantly on maternal and foetal morbidity and mortality [28]. There is a need to determine the renal function of all pregnant women in early trimester as the better the kidney function at the start of pregnancy, the less likely it is to get worse later and vice versa. It has been shown that about one-fifth of women who develop preeclampsia have previously unrecognized CKD [29]. It is therefore imperative for GPs who run antenatal clinics to include at least urinalysis (for proteinuria), urine microscopy (haematuria and urine sediments) and serum creatinine (GFR estimation) during registration of every antenatal client. GPs must of a necessity refer such women to a tertiary centre for joint management by Specialist Obstetricians and the Nephrologist as renal outcome and/or pregnancy outcome may be impacted negatively if not well supervised [30-31].

5.3. Cardiovascular mimicry

As a rule of thumb, any young person with hypertension should be considered to have secondary hypertension of renal origin (fibromuscular dysplasia, atherosclerosis and renal insufficiency) or endocrine disorders (primary aldosteronism, Cushing's syndrome and pheochromocytoma) until proven otherwise and should be thus evaluated [32]. Such young people (usually <30 years) present with difficult to control severe hypertension (drug-resistant hypertension), non-dipping ambulatory blood pressure, or the presence of hypertension-mediated organ damage [33].

Important examples of renal insufficiency include chronic glomerulonephritis (CGN), focal segmental glomerulosclerosis (FSGS) and autosomal dominant polycystic kidney disease (ADPKD). For ADPKD, the patient is usually a young person presenting with any of hypertension, loin pain and haematuria to the clinic or Emergency Room for the first time while CGN and FSGS (usually presenting with severe hypertension, body swelling and changes in the urine appearance) account for 32.7% of diagnosis in individuals who are ≥12 years of age [34-35].

Resistant hypertension, as seen in young people can be confused with some tropical infections/parasitaemia which patients and attending healthcare workers may confuse as poorly treated or resistant malaria fever or typhoid fever. This much has been observed by us in our local setting where severe headache, internal heat and insomnia are among the main symptoms. Unfortunately, by the time some reached the Nephrologist, CKD had set in. Indeed, some authors have tried unsuccessfully to find a direct cause and effect relationship between malaria parasitaemia and hypertension thus ending with a conclusion of epidemiological association at the moment [36-37]. GPs must be wary of young persons with hypertension, regardless of fever or related symptoms and screen for CKD as a matter of first principle.

From time to time, the CKD patient may present to the Emergency Room with acute dyspnea that may be attributable to sudden cardiac pump failure, rapid accumulation of fluid, "flash" pulmonary oedema associated to ARVD. This may be readily confused with left ventricular failure (LVF) which present in very similar scenario but require an entirely different line of management. Incidentally, both usually have very severely elevated blood pressure and orthopnoea.

Pulmonary oedema of renal origin must be promptly differentiated from oedema of cardiac origin as the former recovers dramatically with haemodialysis [38]. A history of paroxysmal nocturnal dyspnoea, presence of third heart sound and elevated jugular venous are helpful in arriving at a quick bedside diagnosis of LVF. A related form of renal-induced pulmonary oedema is hypertensive flash pulmonary oedema (aka "flash" pulmonary oedema) which is a phenomenon that is common among CKD patients in the 5th to 6th decade of life who have developed bilateral renal artery stenosis as a result of atherosclerotic renovascular disease (ARVD) [39-40].

It is characterised by recurrent and recalcitrant pulmonary oedema in the absence of a recognised primary cardiac pathology. It arises from rapid elevation of the left ventricular end diastolic pressure and is usually associated to elevated blood pressure at the time of occurrence hence the alias, "hypertensive flash pulmonary oedema". All middle aged people with recurrent pulmonary oedema should be investigated for ARVD.

Another cardiovascular disease of importance that CKD can mimic is congestive cardiac failure as both diseases could present with symmetrical leg swelling, easy fatigability and constitutional symptoms such as reduced appetite, vomiting and generalised body weakness. However, the pathogenetic rationale for shared symptoms differ. Aside this, evidences have shown a sort of back and forth relationship between CKD and CCF as one can worsen the other and vice versa [41].

5.4. Neurological mimicry

All patients presenting with stroke should be screened for CKD as it is an independent risk factor for both ischaemic and haemorrhagic stroke. A recent meta-analysis incorporating data from 33 studies reported a 43% independent risk of stroke with eGFR <60ml/min/1.73m^2 in the predialytic population [42]. Following acute ischaemic stroke, advanced CKD has been associated with a higher risk of haemorrhagic transformation [43]. Stroke can mask the CKD and lead to unexpected mortality. Individuals with seizures and coma should also be screened for CKD to rule out stroke mimics of which CKD is one [44]. This is because uraemic encephalopathy can mimic stroke in rare cases hence requiring a high index of suspicion [45].

Lesson: CKD can mimic practically any disease, hence routinely check renal function in all new admissions

6. Tip number 5: CKD in children

In the paediatric age group, between 50 and 70% of CKD arise from congenital anomalies of the kidney and urinary tract (CAKUT) that presents histologically as tubulointerstitial nephritis [46-47]. While hypertension, haematuria and body swelling are among the more obvious clinical features expected, they do not readily manifest in children until the latter stages. Worse still, children normally don't have enough insight to appreciate changes in their body and tell their parents. GPs therefore have to be on the lookout for early pointers such as face and/or body swelling, unexplained anorexia, changes in urinary frequency, enuresis, persistent headaches, persistent nausea and vomiting, stunted growth, and poor academic performance. Table 3 provides an abridged but useful quick reference and guide for likely aetiology of common renal symptoms among children.

Table 3 CKD clinical parameters and probable aetiologies in children

Clinical parameter	Probable aetiologies
Smoky urine	Glomerulonephritis, [49] Alport syndrome, [50] papillary necrosis [51]
Family history of CKD	ADPKD, [52-53] ARPKD, [52-53] glomerulonephritis, [54] Alport syndrome, [55] cystinosis, [56] Fabry's disease, [57]
Oligohydramnios	Urinary tract anomalies (familial tubal agenesis, bilateral renal hypoplasia, PUV), [58] ADPKD, [58] ARPKD [58]
Hypertension	ADPKD (hypertension develops at about 4th decade of life), [59] ARPKD (hypertension develops in the first months of life), [60] glomerulonephritis [61]
Recurrent urinary tract infections and/or kidney stone	CAKUT (PUV, one kidney, mal-positioned kidney), [62] nephrolithiasis, [63] reflux nephropathy, [64] medullary sponge kidney [65]
New onset enuresis in children	Overactive bladder/dysfunctional voiding, [66] cystitis [67]
Recurrent haematuria	Papillary necrosis, [51] TIN, glomerulonephritis, [68-69] thin basement membrane disease, [70] nephrolithiasis, [71] urinary tract infection, [71] cystic kidney diseases [71]

ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; CAKUT, congenital anomaly of the kidney and urinary tract; CKD, chronic kidney disease; PUV, posterior urethral valve; TIN, tubule-interstitial nephritis

Lesson: A high index of suspicion is required to diagnose CKD among children

7. Tip number 6: CKD with normal blood pressure

CKD is generally associated with high blood pressure due to loss of renal tubular ability to excrete salt and water in response to elevation of intravascular pressure. However, GPs need to be aware that some cases of CKD may present to them with normal blood pressure. This is because such cases are associated with impairment in tubular salt reabsorption which usually manifest as salt-losing nephropathy [48]. Examples include obstructive nephropathy, analgesic nephropathy, sickle cell nephropathy, early stages of diabetic nephropathy, HIV-associated nephropathy, gouty nephropathy, tubulo-interstitial nephritis from heavy metal poisoning, IgA nephropathy among others. Rather than the assured, "all is well", clinical suspicion should be further heightened if the patient has normal or even excess urine output and supposedly normal kidney size on scan. All of these are part of the confusing features of salt-wasting nephropathy.

Lesson: Do not disregard patients with elevated serum creatinine on account of any or a combination of normal blood pressure, normal urine volume, absence of body swelling and normal renal size on ultrasound scan.

8. Conclusion

Early referral remains a desirable cost effective means of managing CKD whose potential needs to be explored and maximally deployed as it affords Nephrologists timely access to CKD patients with resultant prevention, or delay in onset/progression to ESRD.

With the continuing attrition in the number of Nephrologists globally and more particularly in developing countries, concerted efforts must be made to equip GPs and facilitate collaboration between them and nephrology units in order to take advantage of their strategic role as first contacts with "potential" CKD patients and thus mitigate the relentless rise in the prevalence of CKD.

This can be achieved by establishing an unfettered two-way communication between the renal team and the GPs. Feedback from the Nephrologist affords the GP the opportunity to learn how best to handle the next case using current guidelines. This channel can also be deployed for hands-on, real time, prompt diagnosis of suspected cases and early management with the Nephrologist offering expert guidance via phone, email or social media handles (WhatsApp, snapchat etc.).

In addition, simple, step-by-step protocols on CKD diagnosis, identification of complications, investigations and management priorities can be developed into charts, pamphlets and multimedia devices for placement in primary healthcare centres, private clinics and secondary healthcare facilities for quick references. Table 3 presents an example of a quick reference chart on the most likely aetiology of specific groups of symptomatology that may be useful for GPs who work in children units.

Compliance with ethical standards

Disclosure of conflict of interest

The author has no conflict of interests related to this publication.

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