



Emperor's syndrome in the COVID-19 era: Time for patient-centered nephrology?

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Abstract

The coronavirus disease-19 (COVID-19) pandemic has been a wake-up call in which has forced us to react worldwide. Health policies and practices have attracted particular attention in terms of human and financial cost. Before COVID-19, chronic kidney disease was already considered a risk multiplier in patients with diabetes and hypertension, the two now being the major risk factors for COVID-19 infection and adverse outcome. In contrast to the urgent need for action, the nephrology field is considered to be in a state of stagnation regarding the management of chronic kidney disease patients who still experience unacceptably high morbidity and mortality. Ironically and paradoxically in a field lacking robust clinical trials, clinical practice is driven by guidelines-based medicine on weak evidence. The Emperor's syndrome, referring to Hans Christian Andersen's fairy tale, has been described in medicine as voluntary blindness to an obvious truth, being a weak evidence-based therapeutic intervention or weak health care. A promising positive example of improving heart and kidney outcomes is the emerging treatment with sodium-glucose cotransporter 2 inhibitors. COVID-19 could boost actions for patient-centered care as a positive shift in nephrology care.

Key Words: Emperor's syndrome; Chronic kidney disease; Guidelines-based medicine; Patient-centered care; COVID-19; Evidence-based medicine

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Core Tip: In chronic kidney disease mortality is still unacceptably high. Despite many "whistle-blowers" of a "naked" Emperor (healthcare, polypharmacy without robust

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evidence), the change in clinical practice is slow. Examples are the absence of patient participation in the decision-making process, the low percentage of peritoneal dialysis in Europe and the United States, and the lack of algorithm-based therapeutic interventions. Sodium-glucose cotransporter 2 inhibitors are a positive example of evidence-based multitask treatment. The coronavirus disease-19 pandemic is a good time for reflection and action regarding a shift to patient-centered care in nephrology.

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INTRODUCTION

The last decades have witnessed the rise of two major health problems, the “non-communicable diseases” (namely cardiovascular disease, cancer, chronic respiratory disease and diabetes)^[1], and global pandemics, the most recent being coronavirus disease-19 (COVID-19)^[2]. Chronic kidney disease (CKD) although not listed in the above, is a risk multiplier for cardiovascular morbidity and mortality^[3] and is thus emerging as a global cause of death^[4]. Only recently a promising therapeutic treatment in CKD management has emerged due to the beneficial effects of sodium-glucose cotransporter 2 inhibitors on heart and kidney outcomes^[4].

Apart from this foreseen emerging treatment, the field of nephrology regarding CKD management suffers from stagnation, due mainly to a lack of robust clinical trials for clinically meaningful endpoints, or lack of positive results^[5]. There are also factors inherent to CKD, such as the high percentage of older patients with many comorbidities who are excluded from randomized controlled trials^[6], and the complex pathophysiology of the interaction of heart kidney adverse outcomes^[7]. Traditional cardiovascular risk factors (arterial hypertension, diabetes mellitus, and dyslipidemia) cannot explain the increased morbidity and mortality, so other factors related to CKD per se are considered to be implicated, such as oxidative stress, uremia, and inflammation, marking CKD as a prototype disease of premature ageing^[8]. A major contributor to mortality is also considered to be mineral and bone abnormalities that accompany CKD, leading to accelerated atherosclerosis, vascular and heart valve calcification, collectively described as CKD-mineral and bone disorder^[9].

THE PROBLEM

Ironically and paradoxically, in this complex field of CKD which lacks robust evidence, the contemporary nephrologist is called to manage CKD patients, who are at very high risk of cardiovascular morbidity and mortality, especially in those with end-stage renal disease, with guidelines-based medicine produced from weak evidence^[7]. Furthermore, during the decision-making process the patient is not in the center of this process, but is a passive recipient^[10].

This also holds true for the choice of renal replacement treatment (hemodialysis or peritoneal dialysis) which is guided in major part by the healthcare policy^[11]. The COVID-19 pandemic is like a hurricane that besides devastation provides the dynamic for changes in many fields, political and medical^[11,12]. In this context, it has provided a wake-up call in relation to peritoneal dialysis (PD), being as high as 85% in Hong Kong with a PD-first policy, and < 15% in the rest of the world. PD offers an “at home” therapy which diminishes the risk of contamination compared to hemodialysis in specialized hemodialysis centers, but at the same time poses less financial burden and offers time flexibility in patients’ lives^[11].

This situation of voluntary blindness to an obvious truth in the medical field, already described as “The Emperor's clothes syndrome”^[13] refers to the homonymous fairy tale by Hans Christian Andersen, where the Emperor (healthcare) is naked yet nobody dares to cry it out.

Actually there have been voices that “cried out” but they are muted in clinical practice. In the present article we highlight different aspects that contribute to the

observed “Emperor’s syndrome” in the clinical management of CKD patients and suggest a paradigm shift toward patient-centered care. We perceive patient management from 3 perspectives, the historical perception of the triangle “disease, therapist, patient”, the medical view and the patient’s view.

HISTORICAL PERCEPTION

Looking back at the timeline of the history of medicine^[14], the perception of the “disease, therapist and treatment” has changed drastically from a “patient-centered” view to “evidence-based” medicine. The turning point was the “Germ theory of disease” in the 19th century, which changed the perception of disease from a “holistic view” as an “imbalance” inside the organism to a “specific cause for a specific disease”. Together with this change of view, the treatment approach shifted from a “holistic” view that aimed to “restore” the balance to a narrow approach that targeted the specific cause of the disease. The patient’s role diminished from an active contributor, through personal beliefs, adaptation and lifestyle choices, to a mere passive recipient of the treatment. He is no longer “unique”, but a “number” in a trial, observational or randomized, which will provide the necessary information to form “guidelines” for the disease^[15].

But are these “Guidelines” at least a solid ground on which to rely upon safely for patient management in the form of Evidence-Based Medicine (EBM)? EBM should integrate the best available evidence from the doctor’s experience and the patient’s point of view. This ideal definition of EBM, as introduced by Professor Sackett *et al*^[16], was at the heart of medical practice by Hippocrates (460-370BC), the Greek Father of Medicine^[17]. He instructed doctors to analyze pre-existing data, communicate with the patient and adapt treatment to the individual patient, who is considered unique and called to participate actively in the treatment through changes in lifestyle patterns^[17].

The clothes of the “naked Emperor” (our healthcare) is what we consider nowadays EBM since it has been degraded to “Guidelines-based Medicine”^[18]. Furthermore, Professor Ioannidis emphasized the fact that EBM has been hijacked^[19] in our modern times, since medicine, healthcare, science denialism and quacks provides a complex interplay that leads people astray in their life choices, including health.

It seems that history has made circles in this perception. “Authority” based Medicine of the Past, under the leadership of Hippocrates, Galen and Aristotle, has been replaced by “Guidelines” of contemporary EBM. The homology is that as contemporary “Guidelines” are followed blindly, Galen’s and Aristotle’s statements were not contradicted by their successors, given their prestige and “authority”, even though, ironically, both actively encouraged experimentation and the questioning of established theory^[20].

MEDICAL POINT OF VIEW VS PATIENTS’ VIEW

At present, the patient is regarded as a conglomeration of different diseases-each demanding a specific treatment, governed by “guidelines” from expert committees. In nephrology, this task is covered by the Kidney Disease Improving Global Outcomes (KDIGO) initiative^[21]. These guidelines have 2 grades of “strength of recommendation”, 1 for “strong” and 2 for “weak” (equals suggestion). Each of them is accompanied by a letter (A, B, C, D) corresponding to a level of “Quality of Evidence”, respectively “High”, “Moderate”, “Low” and “Very Low”. Therefore, there are 8 options for each guideline, plus “statements that are not graded” as expert opinion.

PRESENT EXAMPLES OF GUIDELINE-DRIVEN CLINICAL PRACTICE

Hyperphosphatemia: A frequent occurrence in advanced CKD, carrying the fear of accompanying phosphate (Ph) cardiovascular toxicity. The KDIGO 2017 update suggests lowering Ph levels to the normal range (2C)^[9]. This can be achieved with Ph binders, drugs that modify Ph migration from bone *via* parathyroid hormone control, diet and dialysis modification. Despite the “suggestion” and the accompanying “low quality of evidence (C)” for the use of Ph binders in the CKD population, in the real world the corresponding pill burden (average number 19) represents a major burden

for patients in their daily life^[22] and a burden for the healthcare system in terms of financial cost^[23]. Even more frustrating is the fact that there is no definitive proof that “correction” of hyperphosphatemia translates into improved outcomes, such as cardiovascular and all-cause mortality^[24].

Furthermore, the current practice management is not guided by an algorithm based (for example) on the calcification propensity of the individual patient, although the large cross-sectional calcification outcome in renal disease (CORD) study (933 patients from 47 centers in 6 European countries) showed that “Abdominal Aortic Calcification, detected by lateral lumbar radiograph, is associated with several risk factors of uraemic calcification” and thus “could form part of a cardiovascular risk stratification”^[25]. Of note, in the CORD study “19% of patients had no visible calcification in their abdominal aorta, even though some of them were > 80 years of age”. Despite the implication that “the ‘non-calcified’ patients have some typical biochemical and/or genetic features that protect them from calcification” and the strong prognostication role of abdominal aortic calcification as a simple clinical tool for mortality^[26], there is actually scientific paucity regarding in-depth investigation of the pathophysiology and clinical management of the “non-calcifiers”. The non-stratification of the calcification propensity could also potentially annulate therapeutic strategies, for example manipulation of serum magnesium^[27], or pharmaceutical parathyroidectomy by cinacalcet, as in the EVOLVE trial^[28].

Dyslipidemia: A very significant and modifiable factor for cardiovascular morbidity and mortality in the general population with high prevalence in the CKD population, dyslipidemia is characterized by high triglycerides, low high-density lipoprotein-cholesterol and altered lipoprotein composition^[29]. In the general population, the main culprit is considered to be low-density lipoprotein-cholesterol which is targeted with distinct drug classes (statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 inhibitors) alone or in combination, to ever decreasing lower levels^[30]. Although there are some sceptics regarding the use of statins in the general population, suggesting that these drugs stimulate atherosclerosis and heart failure^[31], in end-stage renal disease the question becomes even harder “Should Statins Be Banned from Dialysis?”^[32]. This controversy derives from the fact that the apparent benefit in cardiovascular risk of statins in the general population diminishes as renal function declines and is almost null in maintenance dialysis patients. This led to the KDIGO 2013 suggestion that statins should not be stopped in dialysis patients if already prescribed (2c), but should not be initiated either (2a)^[33].

In real world practice, nephrologists still widely prescribe statins in dialysis patients, which are considered safe and effective drugs^[34], even though a recent observational study suggested that statins may promote vascular calcification in CKD patients^[35].

On the other hand, much cheaper, pharmaceutical or not, ways of reducing cardiovascular risk are not promoted. For example, as shown by our group and others, the manipulation of serum and dialysate magnesium (Mg). Serum Mg, driven in part by dialysate Mg, is inversely associated with vascular calcification^[36], and cardiac hypertrophy^[37]. Mortality has been shown to be correlated both with serum^[38] and dialysate Mg^[39,40]. Another neglected tool is the Mediterranean diet, a magic poly-weapon against all traditional and non-traditional CV risk factors^[41]. Although the Mediterranean diet is associated with beneficial surrogate goals (Ph load, oxidative stress, inflammation, metabolic acidosis, blood pressure control, lipid control), cardiac parameters^[42] and possibly even mortality^[43], it is not a goal strongly implemented in clinical practice.

Are patients aware of the statistics and do they take part in the decision-making process? What would their preference be between implementing a Mediterranean type diet, and using multiple drugs for blood pressure, Ph load and lipid control?

Considering hyperphosphatemia and dyslipidemia management as described above, the “naked Emperor” is in front of us in clinical practice when a patient is characterized as “non-compliant” and the prescribed treatment is of low evidence in terms of EBM. Furthermore, there is extensive literature on the notion of patient non-adherence, or non-compliance; these two notions are used in the same context in the bibliography, but today the first is preferred as the second implies doctor’s authority. That is because the literature testifies to a shift in the healthcare perspective from “every patient is a potential defaulter” towards not “labelling” patients as adherent or not and acknowledging patients’ self-knowledge^[44].

A good strategy for “hyperphosphatemia” and “dyslipidemia” management could be to reconcile evidence-based inputs (ideally from robust stratified studies) to patient-centered decisions. Given that CKD patients have multiple co- morbidities and considering the patient as the sum of distinct clinical entities, by targeting each of them

with a guidelines-based approach, do we treat the diseases or the patient^[45]? At the end of the day is personalized medicine just good medicine^[46]?

If patient management is already confusing in the field of nephrology for the reasons stated above along with the difficulties in conducting clinical trials^[47], it becomes even more so considering the scepticism around the experimentation from which guidelines are drawn. Professor Ioannidis in the provocative article “Why Most Published Research Findings Are False”^[48] urges us as doctors to be cautious in the interpretation of the published literature. Furthermore, there is an ongoing debate regarding the acceptance of the *P* statistical value taken as the “bible” for clinical decisions or be more sceptic about it^[49].

CONCLUSION

In a field lacking robust clinical trials, such as CKD, nephrologists are called to manage these high-risk CKD patients with low evidence guidelines-driven medicine and at the same time they do not usually include patients in the decision-making process. The Emperor (healthcare) is naked and although there have been voices that cry out, maybe the hurricane of COVID-19 could serve as a wake-up call for many aspects of the social, political and medical fields.

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