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Caring for patients with kidney disease: shifting the paradigm from evidence-based medicine to patient-centered care

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ABSTRACT

The last several decades have witnessed the emergence of evidence-based medicine as the dominant paradigm for medical teaching, research and practice. Under an evidence-based approach, populations rather than individuals become the primary focus of investigation. Treatment priorities are largely shaped by the availability, relevance and quality of evidence and study outcomes and results are assumed to have more or less universal significance based on their implications at the population level. However, population-level treatment goals do not always align with what matters the most to individual patients—who may weigh the risks, benefits and harms of recommended treatments quite differently. In this article we describe the rise of evidence-based medicine in historical context. We discuss limitations of this approach for supporting real-world treatment decisions in older adults with chronic kidney disease. We conclude by outlining ways in which the evidence-base might be reconfigured to better support real-world treatment decisions in individual patients and summarize relevant ongoing initiatives.

Keywords: evidence-based medicine, patient-centered care, kidney disease, older adults, paradigm

EVIDENCE-BASED MEDICINE

In a 1992 article in the Journal of the American Medical Association, David Sackett, Gordon Guyatt and colleagues described a new paradigm for practicing and teaching medicine that had been developed over the preceding decades at McMaster University in Hamilton, Ontario [1]. Evidence-based
also places a high premium on studies whose results are widely promoted and over other types of study design. It accords special importance to the randomized controlled clinical trial to facilitate comparison of results across studies and populations. These are not intended to substitute for good clinical judgment driving treatment recommendations, with the caveat that evidence is the major force toward a more empiric approach leveraging information from populations to inform the care of individual patients.

Under an evidence-based paradigm, populations rather than individuals become the primary focus of investigation. Treatment priorities are largely shaped by the availability, relevance and quality of evidence and study outcomes and results are assumed to have near universal significance based on their implications at the population level. Evidence is the major force driving treatment recommendations, with the caveat that these are not intended to substitute for good clinical judgment or override patient preferences [2, 3]. Evidence-based medicine accords special importance to the randomized controlled clinical trial as the ‘gold standard’ for comparing interventions and has promoted its primacy over other types of study design. It also places a high premium on studies whose results are widely generalizable and has fostered the science of meta-analysis and systematic review to facilitate comparison of results across studies and populations.

The meteoric rise of evidence-based medicine over the last several decades is perhaps best understood in the wider context of other powerful forces shaping medical practice, teaching and research over the same time period. These include the expansion of commercial interests in medicine, the development of the modern drug approval process, the growth of professional societies and organizations, the emergence of clinical epidemiology as a distinct field of investigation, the introduction of performance measurement, the growth and commercialization of medical publishing and the explosion of clinical practice guidelines. Collectively, these interrelated developments have all helped to shape the practice of evidence-based medicine while both supporting and benefitting from its entrenchment as the dominant paradigm for clinical research, teaching and practice [4–12].

The principles of evidence-based medicine are integral to contemporary approaches to defining, classifying and managing patients with chronic kidney disease (CKD). Evidence-based clinical practice guidelines developed by KDIGO [13] and recently updated by K/DOQI [14–16] eschew mechanistic disease definitions based on underlying pathophysiology in favor of a population-based or ‘public health’ approach to disease definition, risk stratification and management [16, 17]. Under an evidence-based paradigm, a uniform population-based approach to disease definition, classification and management for all patients is supported by the observation that the relative risks of death and end-stage renal disease (ESRD) within pre-defined risk strata are roughly similar across populations and in different patient groups [16, 18]. This approach has provided valuable information about the population-level implications of different levels of estimated glomerular filtration rate (eGFR) and proteinuria and has supported the evolution of a uniform and systematic approach to care, research and policy formulation.

**LIMITATIONS OF EVIDENCE-BASED MEDICINE**

Despite the broad and sustained appeal of evidence-based approaches to clinical care and research, population-level treatment goals do not always align with what matters the most to individual patients—who may weigh the benefits and harms of treatments quite differently [7, 19]. Especially in medically complex patients and those with functional impairment and/or limited life expectancy it will often be neither feasible nor desirable to follow evidence-based treatment recommendations for all health conditions present [20–22]. In other situations, evidence is simply not available to guide specific treatment decisions that arise in the clinical setting, or does not provide strong support for one treatment strategy over another. In all of these instances, the scientific evidence may provide no better grounds for decision-making than the ‘intuition, unsystematic clinical experience, and pathophyslogic rationale’ [1] that it was intended to replace and may even distort the care of individual patients by favoring interventions that do not support their goals [23].

The potential limitations of evidence-based medicine often come into the sharpest focus when caring for older adults [20, 24–27]. Clinical practice guidelines and the evidence on which they are based are usually constructed with single health conditions, risk factors and treatments in mind. However, the majority of older adults have more than one health condition. The application of treatment recommendations from evidence-based clinical practice guidelines focusing on single health conditions to the care of complex older adults in real-world clinical settings can translate into infeasible treatment regimens, unintended harms and uncertain benefits [21, 25, 28].

**LIMITATIONS OF EVIDENCE-BASED MEDICINE IN CARING FOR OLDER ADULTS WITH KIDNEY DISEASE**

Older adults account for a significant proportion of the overall population with CKD and kidney disease is highly prevalent at older ages [29, 30]. In this section, we draw on a recently published framework for caring for patients with complex comorbidity to structure a discussion of the potential limitations of evidence-based medicine in caring for older adults with kidney disease [31]. We articulate how critical elements of the contemporary evidence-based approach to knowledge creation and dissemination—including choice of study population, selection of interventions and outcomes and reporting of study results—may not be optimally configured to meet the needs of older adults with this condition.

**Study population**

Not uncommonly, older adults with complex comorbidity are excluded from trials whose primary goal is to evaluate the efficacy or effectiveness of interventions [31–33]. This occurs...
in part because treatment effects can most readily be detected and interpreted in homogenous populations with carefully selected characteristics [34–36]. In many instances it would be inefficient and even unethical to execute a pragmatic trial in a heterogeneous population without first assuring an intervention’s effectiveness in those who are most likely to benefit. However, this practice can create a large disconnect between the characteristics of trial populations and those of real-world populations of older adults in whom the intervention is applied, potentially altering both benefits and harms [37].

This tension is evident when applying the results of trials underpinning contemporary guidelines for the use of acetylcholinesterase (ACE) inhibitors and angiotensin receptor blocking agents (ARBs) in slowing progression of CKD to older adults. Most of these trials did not enroll anyone older than 70, most implicitly or explicitly selected for proteinuria, and most enrolled only patients with diabetes [30]. Although the prevalence of low eGFR and proteinuria both increase with age, the prevalence of low eGFR increases much more sharply so that the majority of older adults with CKD do not have proteinuria. This creates a mismatch between the characteristics of younger trial participants—most of whom have diabetes and proteinuria—and those of older adults with CKD in real-world clinical settings—most of whom have neither diabetes nor proteinuria [30, 38–40].

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) bears perhaps the most relevance to older adults with kidney disease cared for in real-world clinical settings. ALLHAT randomized hypertensive adults aged 55 years or older with at least one other coronary heart disease risk factor to receive chlorthalidone, amlodipine or lisinopril for a mean of 4.9 years. The mean age of trial participants with an eGFR < 60 mL/min/1.73 m² was 70 years [30]. Renal outcomes were incidence of ESRD and/or a decrement in GFR of 50% or more from baseline. In post-hoc analyses of trial results, there was no difference in treatment effects for either end point for patients taking amlodipine or lisinopril compared with those taking chlorthalidone [41]. The trial did not test for proteinuria at baseline or during follow-up, and the negative results of ALLHAT have been attributed to a recruitment strategy that did not select for proteinuria resulting in low rates of progression during follow-up [42]. However it is important to note that while inclusion of older adults unselected for proteinuria would not have supported the typical goals of an efficacy trial—to evaluate for a treatment effect under a best case scenario—this strategy actually serves to increase relevance of the results of ALLHAT to real-world populations of older adults with kidney disease, most of whom do not have proteinuria [30].

**Interventions and outcomes**

Under an evidence-based paradigm, studies typically focus on the relationship of single interventions or risk factors to a narrow set of outcomes, an approach that is not intended to replicate treatment decisions that arise in real-world clinical settings. Research is often framed within a disease-based framework to address a narrow set of questions related to a particular comorbid condition and/or the interests of particular professional groups or specialties [43]. The selection of interventions and outcomes are often guided by their relationship to an underlying disease process and/or practical considerations related to trial design rather than what might be most important to individual patients [9].

A focus on kidney disease-related outcomes such as progression, survival or cardiovascular events may not always address what matters most to individual patients. This is especially true for older adults with CKD who often have a high burden of functional impairment and other comorbidity that may be related to—but not necessarily the direct result of—their kidney disease [44, 45]. The presence of coexisting comorbidity and functional impairment in a patient with kidney disease may critically shape treatment priorities and significantly alter the benefits and harms of disease-related approaches to management. Especially in complex patients, patterns of eGFR loss may often reflect extrinsic factors—such as how sick patients are and how well they are able to maintain kidney function in the setting of other illnesses—rather than the intrinsic course of an underlying kidney disease [46, 47]. In this setting, interventions targeted more broadly at maintaining health may make more sense than those narrowly focused on preserving kidney function. More globally, the high prevalence of other health conditions in older adults with kidney disease may often limit the relevance of a disease-specific approach to research for members of this population.

Although newer trials in nephrology increasingly capture information on non-disease-based outcomes such as quality of life [48], much of the evidence supporting current practices comes from trials that focused only on disease-based outcome measures [30, 49]. Receipt of dialysis is often used as a hard outcome measure in nephrology trials. As both a measure of disease progression and a treatment, use of this outcome has some limitations. Onset of dialysis or ‘treated ESRD’ will not capture patients who reach the advanced stages of CKD and are not treated with dialysis or kidney transplant, which may occur more commonly in older adults [50]. Use of change in eGFR or doubling of serum creatinine over time as measures of progression relies on a simplified model of the trajectory of kidney disease that does not account for heterogeneity in patterns of renal function loss both between different patients and within the same patient over time [47, 51, 52]. There is also growing circumspection about the utility of proteinuria as a surrogate outcome measure [53].

ESRD prevention trials often lump measures of progression such as ESRD onset with death to form a composite outcome [30]. Use of composite outcomes can help to support trial feasibility by minimizing recruitment targets and/or follow-up time needed to detect a statistically significant treatment effect. However, this practice overlooks the distinct implications that each outcome—and the relationship between them—may have for individual patients. ESRD often takes many years to develop and the majority of patients with kidney disease do not survive long enough to reach the advanced stages of disease, especially at older ages [18, 54, 55]. From the patient perspective, information on the risk of both death and ESRD is needed in order to estimate their likelihood of developing ESRD during their remaining lifetime [55]. For example, while risk of ESRD increases exponentially as eGFR declines for patients of all ages [18], and
the risk of ESRD is roughly similar for patients of different ages with similar levels of eGFR, the competing risk of death is much higher for older patients than younger patients with the same level of eGFR [18]. Thus, compared with their younger counterparts with similar levels of eGFR, older adults will be much less likely to reach ESRD during their remaining lifetime [55]. This appears to be true even after accounting for potential age differences in treatment practices for ESRD [50].

**Results reporting**

It is important to recognize that the same source data can be presented differently depending on the intended message and audience [56]. The language of evidence-based medicine has largely evolved to summarize the role of risk factors and interventions in relation to a single or limited number of outcomes at the population level, rather than to support the treatment decisions of individual patients in the clinical setting. Like outcomes, treatment effects are assumed to have more or less universal significance under an evidence-based paradigm. A common practice is to ascribe significance to any statistically significant level of risk or relative risk reduction with little consideration for the magnitude of absolute risk or absolute risk reduction or the significance of the outcome to patients [5, 57, 58]. This approach can work well when the goal is to compare risks or treatment effects across populations but may be less helpful in guiding the care of individual patients. The same reduction in relative risk can translate into diverse benefits for individual patients depending on their baseline risk and individual patients may weigh a given reduction in absolute risk very differently [27, 28, 59].

Under an evidence-based approach, prognostic information is typically presented in terms of relative and absolute risk of death rather than life expectancy. Information on heterogeneity in life expectancy within groups is almost never reported, in part because reliable information on life expectancy may require a follow-up time that exceeds the duration of most studies. Nevertheless, an understanding of life expectancy—and the degree of uncertainty surrounding estimates thereof—is often crucial in estimating the benefits of recommended interventions for individual older adults [60, 61]. Although presenting information on ‘average’ or ‘median’ life expectancy represents a step in the right direction, information on distribution of survival times (e.g. 25th–75th percentiles) is needed in order to convey information on the degree of uncertainty around estimates of longevity and to provide a more realistic picture of the importance of individual risk factors when placed in a broader context [62].

Clinical trials typically report relative and absolute risk reduction over the course of the trial—an often arbitrary time period that may not be meaningful to individual patients—and almost never report time-to-benefit [58]. For patients and providers, knowing the minimum time period needed for a benefit to accrue may be as or more important than knowing the treatment effect over the course of the trial. Information on time-to-benefit may be an especially important consideration in patients with limited life expectancy—who are unlikely to benefit from an intervention whose time-to-benefit exceeds their own life expectancy [63, 64].

These inherent tensions are evident when considering the design of trials supporting the use of ACE inhibitors and ARBs for slowing progression of kidney disease. Most trials deliberately recruited patients at high risk for progression to ESRD precisely because the expected time course for progression in lower risk patients would exceed the maximum feasible follow-up time. Because rates of ESRD have generally been quite high among patients enrolled in trials demonstrating an effect for ACE inhibitors and ARBs on progression to ESRD, the relative risk reduction conferred by these agents yielded relatively low numbers-needed-to-treat (NNTs) to prevent one case of ESRD in trial populations, ranging from ~9 to 25 over the course of the trial [38].

To evaluate how generalizable these results might be to older adults in real-world clinical settings, we conducted a simulation study in which we applied a treatment effect similar to that achieved in major trials (30% relative reduction in the risk of ESRD over 3 years) supporting the use of ACE inhibitors and ARBs for ESRD prevention to a clinical population of older adults with kidney disease [38]. There was a striking degree of variation in the absolute risk of ESRD among members of this real-world cohort across different levels of eGFR and proteinuria resulting in dramatic differences in the NNT, ranging from 16 for those with the highest, to 2500 for those with the lowest baseline risk of ESRD. The vast majority of cohort members belonged to groups for whom the NNT was well above 100—much higher than reported in clinical trials.

It is important to recognize that when we extrapolate the results of these trials to patients at lower risk for ESRD, we make the implicit assumption that similar benefits will accrue over longer periods of time. Whether this is a fair assumption would depend on whether the intervention can be expected to have similar efficacy in lower risk populations. It would also depend on their likelihood of reaching ESRD over the course of treatment—a quantity that can be expected to vary as a function of how fast they are losing renal function and their competing risk of death among other things. We therefore extended the time frame for follow-up to 10 years and assumed that patients would continue to derive a similar benefit over this longer period of time (or over their remaining lifetime if they died within 10 years). Even after extending the observation period to 10 years—which exceeded the remaining life expectancy of 68.6% of cohort members—the NNT was still very heterogeneous across groups ranging from 10 to 435, and 73% of cohort members still belonged to groups for whom the NNT exceeded 100. These findings highlight the potentially large disconnect between the benefits attributed to interventions based on the results of clinical trials conducted in younger selected trial populations at high risk for ESRD and real-world clinical populations of older adults with CKD.

**P A T I E N T - C E N T E R E D C A R E**

While especially relevant when caring for medically complex patients or in situations where there is no clear ‘right’ treatment (so called ‘preference-sensitive’ decisions), more ‘patient-centered’ paradigms are gaining credence as a viable...
complement, or even alternative, to evidence-based medicine across a broad range of settings [3, 22, 65, 66]. Key elements of a patient-centered approach to care include integrating available information on the likely benefits and harms of relevant treatments for individual patients with information on their prognosis, values and preferences [64]. Domains identified as important in designing patient-centered care plans include patient preferences, the quality and applicability of evidence, patient prognosis, clinical feasibility and integration of different treatments [58]. Under a patient-centered—or person-centered—paradigm, the availability, relevance and quality of evidence may still play an important role in shaping treatment decisions, but the unique circumstances, goals and values of individual patients move to center stage. These considerations then critically inform the interpretation and application of existing evidence to clinical practice as well as the generation of new evidence [19, 22, 65–67].

Acknowledging and communicating uncertainty and integrating information about uncertainty into individual treatment plans are integral to patient-centered models of care [62]. Stronger efforts to build an evidence-base to better support patient-centered care will not eliminate inherent uncertainty about illness trajectory, prognosis and treatment in individual patients. However, when we begin not with the evidence but with the patient, what constitutes an ideal body of evidence may assume a much different shape [20, 58]. Below we outline key considerations in reconfiguring the evidence-base to better support the care of individual patients in the clinical setting.

First, recruitment strategies could be designed to optimize relevance and applicability to real-world clinical settings [68–70]. Second, choice of interventions and outcomes could be more strongly guided by what might be most useful to patients and their providers in real-world clinical settings. Studies narrowly focused on single diseases or risk factors—such as CKD—will usually be less helpful than those focused on constellations of diseases or on cross-cutting health conditions like functional impairment and frailty that may not be closely tied to an underlying disease process [43, 70, 71]. Studies that compare a range of treatments available in real-world clinical settings will generally be more informative than studies that compare a single treatment to placebo. Strategies for outcome selection could be guided by an understanding that individual patients may value different outcomes. In general, studies that address outcomes with broad relevance to patients such as symptom burden, physical and cognitive function, social participation and health-related quality of life will be more helpful than those focused on one or a few select disease-related outcomes [20, 70, 72, 73]. Third, strategies for reporting results could be guided by an understanding that outcomes—even so-called ‘patient-centered’ or ‘patient-reported’ outcomes—and treatment effects do not have universal significance and that demonstration of efficacy or effectiveness alone may be insufficient to support treatment decisions in individual patients. Including information on survival time (or life expectancy), absolute risk reduction (or NNT) and time to benefit, preserving information on competing risk [74] and reporting heterogeneity in risk and treatment effects [75] whenever possible will provide the kind of flexibility needed to apply study results to the care of individual patients [58, 60].

Several initiatives are currently underway to support a more patient-centered approach to knowledge creation and patient care. First, and perhaps most importantly, there is now growing recognition of the importance and power of engaging patients and their representatives in setting research priorities and shaping the design, conduct, interpretation and dissemination of study results. Increasingly, organizations seeking to promote a patient-centered approach to research and clinical care actively solicit input from members of the public and other stakeholders. The National Institute for Health and Care Excellence (NICE) in the UK has developed multiple avenues for stakeholder involvement in shaping clinical practice guidelines including public meetings, committee membership and stakeholder registration (https://www.nice.org.uk/about/nice-communities/public-involvement). In the USA, the Patient Centered Outcomes Research Institute (PCORI) has spearheaded initiatives to promote patient-involvement in research endeavors and participation in the research review process and has already sponsored several projects of relevance to patients with kidney disease (www.pcori.org) [76, 77]. It is hoped that bringing patients and their representatives to the table as an integral part of the research enterprise will help to increase the relevance of research to patients in real-world settings and speed the pace of knowledge creation and implementation. Novel approaches to evaluation will likely be needed to gauge the effectiveness of this approach in supporting patient-centered care.

Second, there is growing interest in more flexible approaches to study design including the use of pragmatic trials and observational data from real-world clinical settings. Pragmatic trials are intended to assess the effectiveness of interventions in real-world practice [78]. Typically, these trials use broad eligibility criteria and recruit patients from a variety of practice settings to ensure inclusion of patients similar to those for whom the intervention is ultimately intended. Patients enrolled in these trials often continue to receive usual care which may mean modifying or omitting procedures such as blinding that are central to the design of efficacy trials. Threats to the validity and feasibility of pragmatic trials include lack of adherence to treatment, loss to follow-up, need for very large sample sizes and potential for bias [78]. Although subject to residual confounding, the use of quasi-experimental designs to leverage observational data from the electronic health record is emerging as a promising approach to evaluating the effectiveness of interventions across a wider range of settings and patient subgroups that may be beyond the reach of clinical trials [79].

Third, there is now growing appreciation of the importance of integrating shared decision-making into evidence-based medicine [23, 80, 81]. Newer evidence-based clinical practice guidelines make explicit reference to the importance of patient values and preferences in guiding treatment decisions [2] and there are ongoing efforts to integrate shared decision-making into clinical practice guidelines [81]. Expanding the scope of training in evidence-based medicine to encompass decision science and shared decision-making may also be helpful [23].
Fourth, there has been progress in defining cross-cutting health outcomes not tied to particular underlying disease processes that could serve as universal health outcomes. In 2011, the National Institute on Aging convened an expert panel to discuss appropriate health outcome measures for older adults with multimorbidity [82]. The panel suggested assessments of general health, pain, fatigue and physical health, mental health and social role function, along with gait speed measurement be adopted as ‘universal’ health outcome measures in older adults and recommended several specific instruments. Other important domains identified as potentially important included disease burden, cognitive function and caregiver burden.

Finally, there is growing interest in methods of healthcare delivery that are more responsive to patients’ needs. Available evidence suggests that the patient-centered medical home model developed in the USA may enhance access to care, improve the management and coordination of chronic disease care, reduce costs and lead to improvement in patient satisfaction and experience of illness [83–86]. A recent survey conducted by the Commonwealth Fund reported significant penetration of medical home models in Europe [87]. While originally intended as a primary care model, there is growing interest within the nephrology community in the potential relevance of this model for patients with advanced kidney disease [88, 89].

CONCLUSION

In summary, a more patient-facing approach to research design, reporting and evaluation will be needed in order to build an evidence-base that can better support patient-centered treatment decisions for those with CKD. Most likely this will require conceptual models that are less disease-specific, a willingness to engage patients and their representatives in the research enterprise and a more flexible approach toward study design and evidence evaluation.

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Enteric hyperoxaluria: an important cause of end-stage kidney disease

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ABSTRACT

Hyperoxaluria is a frequent complication of inflammatory bowel diseases, ileal resection and Roux-en-Y gastric bypass and is well-known to cause nephrolithiasis and nephrocalcinosis. The associated prevalence of chronic kidney disease and end-stage kidney disease (ESKD) is less clear but may be more consequential than recognized. In this review, we highlight three cases of ESKD due to enteric hyperoxaluria following small bowel resections. We review current information on the pathophysiology, complications and treatment of this complex disease.

Keywords: inflammatory bowel disease, kidney stones, oxalate, transplantation, urolithiasis

INTRODUCTION

Enteric hyperoxaluria (EH) is a frequent complication of inflammatory bowel diseases (IBD), ileal resection and Roux-en-Y gastric bypass (RYGB) and is well-known to cause nephrolithiasis and nephrocalcinosis. Less well-known, and highlighted here, is that it also contributes to chronic kidney disease (CKD) and end-stage kidney disease (ESKD). The urinary solubility product of calcium oxalate (CaOx), a determinant of the tendency of urine to yield crystals, is 10 times more affected by a rise of urinary oxalate concentration than an equimolar rise in urinary calcium concentration [1]. The prevalence of hyperoxaluria has been estimated at 5–24% of all patients with gastrointestinal diseases associated with malabsorption [2, 3]. Hyperoxaluria is becoming more common secondary to an increase in IBD [4] and bariatric surgery. The associated prevalence of CKD and ESKD is less clear but may be more consequential than recognized. Here we highlight three cases of ESKD due to hyperoxaluria and review the relatively sparse literature on treatment.

CASE 1

A 33-year-old woman was diagnosed with Crohn’s disease at age 17, her course complicated by small bowel infarction due to a volvulus requiring small bowel resection. She developed