

Second Edition

Evidence-Based Nephrology

VOLUME I AND II

EDITED BY

JONATHAN C. CRAIG | DONALD A. MOLONY | GIOVANNI F. M. STRIPPOLI

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Evidence-Based Nephrology

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Second Edition

VOLUME I

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Preface

The synthesis of the totality of evidence in kidney disease was the original challenge we undertook when we conceived of the first edition of this evidence-based nephrology (EBN) textbook, thereby providing students of nephrology and practicing clinicians with a single convenient source of clinical evidence that had been passed through an evidence-based filter. More than 12 years have passed since the first edition, and so it is timely to revisit the challenge in the form of a second edition. The reasons for a second edition are principally three: the scale of new available data is substantial, newer methods of research synthesis have been developed, and there is a renewed focus on consumer engagement in general, including in the evaluation and management of kidney disease.

Scale of new data

Compared to the time of the first edition, the amount of new data is impressive. There are today more than 15 000 randomized controlled trials in nephrology published in approximately 30 000 reports, 11 300 more than in 2009, resulting in more confidence and precision around the estimates of intervention effects and new evidence in areas that were previously mostly evidence-free. These trials have also been summarized in systematic reviews, with over 6500 additional reviews in Medline since the first edition. Much of this new evidence is incorporated in three new sections of this textbook and multiple either new or entirely updated chapters.

Novel methods

Methods to assess the methodological quality of both systematic reviews and other study designs, including nonrandomized (case-control or cohort studies) and diagnostic test studies, have developed since the first edition. In addition, the number of syntheses of cohort studies has increased and the technique of network meta-analysis for comparing more than two interventions both directly (head to head) and indirectly (via a common comparator) has become more developed and is commonly encountered. These

methods assist the summarizing and interpreting of evidence in key areas of decision-making, which is useful to patients, healthcare providers, and policy-makers.

Using these methods, organizations including the Cochrane Kidney and Transplant group and several guideline agencies have committed on a large scale to summarize the evidence and provide timely updates of established and emerging new evidence, making research findings more manageable and reliable for end users. Much of this work has been included in this edition of the textbook. We hope this will allow the end-user to both access best evidence from this diversity of resources as summarized by chapter authors and to become more familiar with how the newer techniques and resources contribute to a practice that is informed by best evidence.

Consumer engagement

Recently, there has been increasing recognition of the critical importance of engaging the end-users in research to ensure relevance and uptake. In particular there have been large-scale efforts to engage patients in all stages of research, including the evidence synthesis process and the dissemination of findings. For example, the Cochrane Kidney and Transplant group now has a patient editor, whose role includes translating scientific outputs into plain language summaries to simplify the “medical jargon” and make evidence easily accessible to people without a medical background, as well as prioritizing review topics. The Standardized Outcomes in Nephrology (SONG) initiative was launched in 2014 to establish the core outcomes to be reported in all trials in chronic kidney disease, based on a consensus among patients, caregivers, health professionals, and policy-makers. This initiative has emphasized patient-centered research and improved clinical outcomes in nephrology, ensuring that the outcomes measured and reported in clinical trials and other forms of research are relevant and meaningful to patients and increase the acceptability, transparency, and generalizability of the results in this population. New studies assessing these

outcomes are now being developed, with advancement of knowledge which could be incorporated into this edition of the textbook.

In short, compared to the previous version published in 2009, this updated textbook includes 20 new chapters and three new sections, covering supportive care and patient-centered care and outcomes. In addition, every chapter that was in the first edition has been extensively updated. Specifically, the new textbook covers epidemiology, acute kidney injury, primary diseases of the kidney, secondary diseases of the kidney, chronic kidney disease and complications, hemodialysis, chronic kidney disease stage 5, peritoneal dialysis, supportive care, transplantation, electrolytes and acid-base disorders, and patient-centered care and outcomes for both adult and pediatric patients. This effort was undertaken by existing and new authors and section editors, whom we would like to thank for their extensive work.

Giovanni Strippoli has joined as the third co-editor of *Evidence-based Nephrology*. Altogether, we hope that we have produced an even better evidence-based nephrology tool, where each chapter provides a clear foundation of the topic that is supported by the best current evidence.

We believe that this updated textbook more broadly covers available evidence and addresses crucial clinical questions regarding the treatment and care of people with all stages of chronic kidney disease, including people undergoing any form of dialysis (hemodialysis or peritoneal dialysis), those requiring kidney transplantation, and pediatric patients.

Inherently a textbook of this nature will always manifest potential limitations. We acknowledge that a textbook is unable to collect all new evidence in real time, and, like all of healthcare internationally, the COVID-19 pandemic did impact this book, specifically the publication timelines as contributors had to contend with major challenges. The inclusion of nonrandomized studies to maximize relevance

and comprehensiveness has added complexity in the methods and may lead to residual uncertainty in the estimate of intervention effects. Finally, we focused on empiric evidence for management decisions and so pathophysiological mechanisms of chronic kidney disease and its treatment were not considered in detail. We have attempted to include economic evaluations where particularly relevant for national and international management guidelines.

In the true spirit of evidence-based medicine, we hope that this edition of *Evidence-based Nephrology* will continue to push the specialty toward greater reliance on the totality of evidence and the generation and utilization of evidence that is the least biased and the most precise to inform clinical decision making. To the material detailed in all the chapters we would expect that our readers will add, through their own judicious application of evidence-based medicine principles, their local context, and incorporate their patients values and preferences, given that objective evidence is rightly only one consideration in the delivery of true patient-centered care. Additionally, a textbook like this can at best be only one of several resources for the evidence-based medicine practitioner, and should be supplemented with current methodologically rigorous and transparent clinical practice guidelines. We hope this effort will provide a core resource for the evidence-based nephrology practitioner who is otherwise limited by time constraints from researching every question that may arise daily in the care of patients.

We certainly wish that students and evidence-based nephrology practitioners will benefit from this updated edition in the search for answers to questions that arise in daily care and their ambition to deliver the best care possible.

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Part 1

Epidemiology

1

An Introduction to the Epidemiology of Chronic Kidney Disease

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Introduction

The purpose of this part of the book is to describe the epidemiology of chronic kidney disease (CKD) across the spectrum of disease, from early detection through to major complications and end-stage kidney disease (ESKD). Fundamental to this is an understanding of what defines CKD. We will therefore begin this chapter by revisiting the 2002 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF/DOQI) guideline, which first proposed a harmonized definition of CKD based on simple laboratory markers. A tremendous amount of data has been accrued since that seminal publication, data which informed the updated CKD classification system by Kidney Disease Improving Global Outcomes (KDIGO) in 2012.

The definition and staging of CKD has generated debate and controversy among the nephrology community. There is confusion surrounding the definition and the classification system. The former is an important, inclusive, and objective definition to describe the state of kidney function and structure which is associated with disease. The latter describes the severity of disease and risk associated with two parameters: level of estimated glomerular filtration rate (GFR) and degree of albuminuria. The classification of CKD is underpinned by the risk of a series of clinical outcomes. The key outcomes in this context are progression to ESKD, cardiovascular, and all-cause mortality. Other outcomes include acute kidney injury (AKI), hospitalization, cardiovascular events, and infections. This chapter provides an overview of the risk relationships between CKD and these first three

well-studied outcomes. We also highlight some of the more controversial aspects of the CKD paradigm: the definition of CKD in older individuals, and strengths and limitations of different filtration markers and GFR estimating equations. These important issues continue to be discussed and debated within the nephrology community. However, it should be acknowledged that patients with kidney disease are looked after by other healthcare providers, including primary care physicians, cardiologists, and gerontologists. Thus, the framework for diagnosis, staging, and risk stratification of patients with kidney disease must be clear and well-communicated to all stakeholders. This is especially pertinent in developing countries, where our understanding of the epidemiology of kidney disease and its risk factors is more limited.

The subsequent chapters in this part expand on these concepts and provide the reader with an up-to-date review of the state of knowledge of the epidemiology of kidney disease. Chapter 2 describes the variety of surveillance mechanisms currently utilized for CKD and ESKD, along with the challenges of obtaining accurate data from around the world. The importance of early detection of CKD and the evidence for population-level screening is discussed in Chapter 4. Chapters 3 and 5 provide an evidence-based approach to prognostication for progression of CKD and the risk of important clinical outcomes such as cardiovascular disease and mortality. Finally, the emerging literature regarding the burden of CKD in disadvantaged populations is described in Chapter 6. Throughout these chapters, a standardized nomenclature for CKD is used to frame the discussions. Hence, that is where we begin this introduction.

Definition of CKD

In 2002 NKF-KDOQI published a guideline proposing a new paradigm for the classification and evaluation of kidney disease [1, 2]. This conceptual framework (Figure 1.1) addressed an unmet need in nephrology: the early identification of patients at risk of either developing kidney disease or progressing to more advanced stages of disease. The NKF-KDOQI working group suggested a new classification system that could categorize the severity of an individual's kidney disease, irrespective of etiology, using simple laboratory parameters. One of the most significant contributions of this work was the harmonization of nomenclature for kidney disease [3]. The term “chronic kidney disease” and its stages would supplant ambiguous terminology such as “azotemia,” “predialysis,” or “renal insufficiency” [4]. The original guideline has had a major impact over the last 15 years or so by facilitating collaborative research endeavors, standardizing clinical and laboratory practices, and informing health policy.

The definition of CKD was further refined by the KDIGO working group in the 2012 guidelines, and is the one used in contemporary clinical practice. KDIGO defines CKD as abnormalities of kidney structure or function, present for at least 3 months, with implications for health [5]. CKD can thus be defined by markers of kidney damage and/or markers of reduced kidney function. GFR is considered the best metric of kidney function and is estimated from the serum concentration of a circulating filtration marker such as creatinine or cystatin C. CKD can be diagnosed by GFR criteria alone if an individual has at least two estimates of GFR below $60 \text{ ml/min/1.73 m}^2$ at least 3 months apart. Even in the presence of “preserved” kidney function ($\text{GFR} \geq 60 \text{ ml/min/1.73 m}^2$), CKD can be diagnosed in the presence of persistent urinary abnormalities such as albuminuria, hematuria, or evidence of tubular dysfunction.

In the absence of any of these factors, an individual can be diagnosed as having CKD if they have a structural abnormality identified on imaging tests, for example polycystic kidney disease, or a histopathological abnormality such as tubulointerstitial disease.

KDIGO proposed a standardized approach to the classification of CKD based on the cause of disease (C), level of GFR (G), and amount of albuminuria (A), the CGA system. The classification and staging of CKD can be done independent of cause, but the guidelines clearly recognized the importance of attempting to ascertain the etiology of CKD. Statements within the guidelines acknowledge the importance of interpreting the GFR and albuminuria results in the context of an underlying cause, as the specific cause may influence the risk or anticipated rate of disease progression. In many cases, however, the cause is unknown or can only be speculated upon based on the presence or absence of key risk factors such as diabetes or hypertension. For many patients a kidney biopsy remains the only means of establishing a firm diagnosis, although recent advances in molecular diagnostics have the potential to overcome this barrier [6]. The clinical focus on GFR and albuminuria for CKD staging is based on iterative studies demonstrating that both parameters are powerful predictors of clinical outcomes. The cross-classification of GFR and albuminuria stages provides a categorization of an individual's risk status (Figure 1.2). The synergistic effect of both risk markers is reflected in the fact that individuals with a combination of reduced GFR and a high degree of albuminuria are at greatest risk for ESKD. It is also evident from this risk classification that the presence of albuminuria is a strong risk factor for ESKD even if the GFR is normal. The thresholds of GFR and urinary albumin to creatinine ratio (ACR) that are used to establish the stage of CKD are based on large population-based studies examining the association between both markers and hard clinical endpoints.

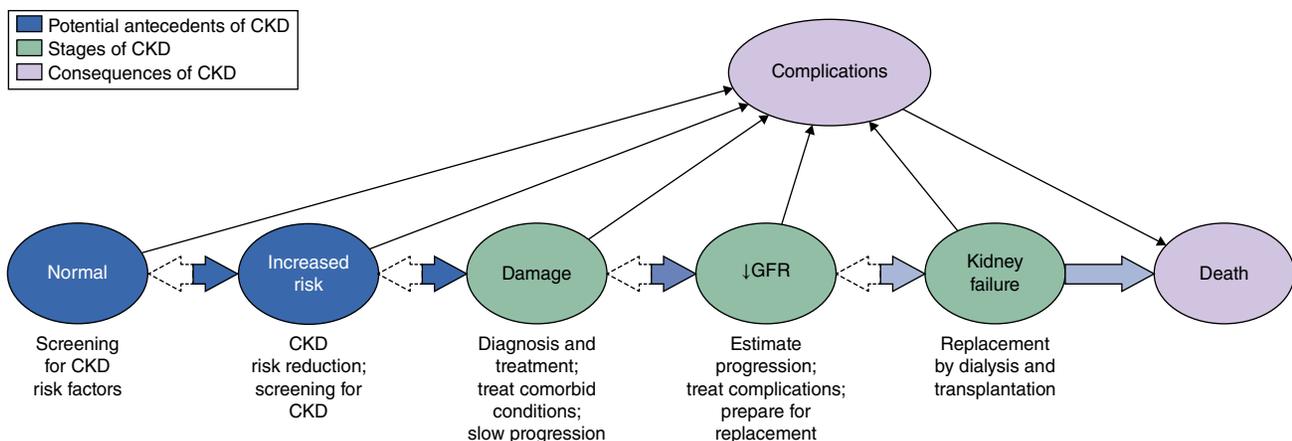


Figure 1.1 Conceptual paradigm for chronic kidney disease. CKD, chronic kidney disease; GFR, glomerular filtration rate.